

ANNUAL REVIEW OF PHYSIOLOGY

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PREFACE

In introducing Volume VI we find
That thoughts, expressed before, are brought to mind
And entered in this preface. Number one,
Our thanks to our reviewers, who have done
A splendid job in bringing up-to-date
(Despite the many hindrances of Fate)
The work in all the fields which we review
In manner ever-challenging and new.
Next may we pause a moment to express
Our deep regret that owing to the stress
Of war and hate the fires of Truth burn dim,
Forsaken for a flaming torch and hymn
In praise of violence that cannot last.
But when this world-consuming fever's past,
We'll find that Truth, although neglected, still
Has had her faithful few, who by their will
Alone have kept her altar lights aglow.
Next we would here our gratitude bestow
Upon McCulloch, Cole, Cattell and Gold,
Who thought to write, but found they could not hold
Time's fleeting footsteps back, and wrest a few
Short moments from his grasp, enough to do
The tasks demanded by the war and us.
Now may we end the things we would discuss
With thanks to printers and to all of those
Who aided from inception unto close
The preparation of this Volume VI.
Our signature we now hereto affix,
And with one last and fondly tender look
We say goodby and hope you like the book.

Pub. Composed for the Editorial Committee by our Editorial Assistant, Miss Esther Davis.



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ERRATA

Volume V, page 10, line 7 from bottom: *for* Heuper, *read* Hueper.

page 14, line 9 from bottom: *for* Heuper, *read* Hueper.

page 148, line 6: *for* muscles is increased, at least, *read*
muscles is increased and epinephrine di-
minishes the myotonic condition, at least.

DEVELOPMENTAL PHYSIOLOGY

BY VIKTOR HAMBURGER

*Department of Zoology, Washington University,
Saint Louis, Missouri*

Except for developmental genetics, which was covered previously (1), the present review will include the experimental embryology of the last two years, since last year's review (2) was limited largely to the physiology of the mammalian fetus. A characteristic feature of the period is the trend towards a more physiological and biochemical understanding of developmental processes. This tendency finds its programmatic expression in Needham's book, *Biochemistry and Morphogenesis* (3). It brings the author's *Chemical Embryology* of 1931 up to date but its most original part is a concise and exhaustive treatment of the problems of embryonic induction in all its ramifications, emphasizing the biochemical point of view. It includes chapters on the organizer in amphibians and in other groups, the relation of induction to genes, to cancer, and to regeneration. It is a valuable source of information, as well as a stimulating introduction to modern problems of developmental physiology.

STRUCTURE OF THE EGG; POLARITY

The most important contribution is that of Holtfreter (4), who gives a detailed description and experimental analysis of the physical properties of an elastic, rather rigid, surface coat in amphibian eggs and early embryos. It originates in the ovarian egg and, later on, binds the surface cells together into a supercellular unit. This elastic intercellular connection accounts, at least in part, for the integration of directed mass movements of cells during gastrulation, neurulation, and other folding processes. Experiments show that wound healing in embryos is initiated by expansion of this coat. Its significance as an osmoregulator is recognized and documented by experiments. It accounts furthermore for a structural polarization of the surface cells which may be the basis for the polarization of epithelia in later stages. This study offers a new and original approach to a variety of fundamental problems. It may, one day, substantiate the stimulating suggestions of F. O. Schmitt (5) concerning the possible morphogenetic role of patterns

of oriented protein molecules on cell surfaces. The fundamental problem of how polarity and bilaterality originate in the egg has been furthered in two instances in which both can be induced by external agents. Whitaker (6, 7) continues the analysis of polarization of the *Fucus* egg caused by ultraviolet radiation. The radiation effect is not mediated by an activation of auxin. Its earliest detectable manifestation is a viscosity increase at the irradiated side. White light counteracts its growth-retarding effect. A new technique of creating steep gradients of chemical agents across the egg is described (8). Pease (9) continues his promising attempt to modify bilateral symmetry in the sea urchin (*Dendraster*) egg by gradients of specific respiratory inhibitors. Obviously the cyanide-sensitive part of the oxidation mechanism, probably cytochrome oxidase, plays an important role in determining bilaterality. Child (10) suggests that polarization in the *Drosophila* egg may be tied up with respiration gradients in the ovary.

PHYSIOLOGY OF GAMETES; FERTILIZATION

Sperm.—A comprehensive review of sperm physiology is given by the National Committee on Maternal Health (11). Important work has been done on the metabolism of mammalian and human sperm (12). Spermatozoa oxidize glucose while in the epididymis (13); but, after ejaculation, oxygen proves to be toxic in high concentrations due to hydrogen peroxide formation. Yet, in spite of the fact that anaerobic glycolysis is the chief energy-yielding process for motility, the human sperm contains a virtually complete respiratory enzyme system (12). X-irradiated sea water decreases survival time of *Arbacia* sperm; direct x-irradiation of sperm reduces fertilizability (14,15). New evidence is given that bat sperm may remain fertilizable in the uterus for several months throughout hibernation (16). X-irradiation of male albino rats affects viability and litter size of offspring; high doses result in early resorption of the fetus (17).

Eggs.—The oxygen consumption of the primary oocytes of the sea urchin *Paracentrotus* is as high as that of the fertilized egg but decreases temporarily during the maturation divisions (18). The osmotic properties of oyster eggs (19) and the intake of ions by a number of marine eggs (20) were investigated. The *Chaetopterus* egg after fertilization shows an increased permeability for water while the rate of oxygen consumption decreases; these processes are

independent of each other (21). The progressive expansion of the fertilization membrane in sea urchin and starfish eggs is not due to osmotic water intake but to intrinsic properties of the membrane itself (22). The osmotic water absorption into the egg capsule of salamanders (23) and the hatching mechanism of salmon eggs (24) were investigated. Hyaluronidase, secreted by or liberated by the sperm, is responsible for the freeing of mammalian ova from the surrounding follicle cells (25, 26). Clowes, Krahll, and co-workers (27, 28, 29) continue their important investigations of the metabolism of sea urchin eggs with a systematic survey of the energy-yielding processes. The total acid-hydrolyzable carbohydrate, glycogen, and protein contents were determined. It was found that during cleavage the energy is probably derived from protein oxidation or a combination of this and carbohydrate oxidation, but that the latter is predominantly utilized in later stages. Cocarboxylase, in a concentration comparable to that of other animal tissues, and cozymase have been demonstrated. The presence of cytochrome oxidase had been established previously; two-thirds of its contents are now found to be localized in the cytoplasm and 12 per cent in the yolk granules (30). Most of the major respiratory enzymes are thus accounted for quantitatively.

Fertilization.—Tyler (31) has successfully adopted an immunological point of view in the analysis of fertilizin, the sperm-agglutinating agent liberated by sea urchin eggs. It is of protein nature and comprises part or all of the gelatinous membrane of the egg. It aids in, but is not necessary for, fertilization. Its agglutinating effect is reversible. It can be transformed into a univalent form by heat, x-, and ultraviolet radiation (32), thus losing its agglutinating but retaining its sperm-combining capacity. An antifertilizin can be extracted from sperm which reacts with fertilizin in the manner of antigen and antibody. It reduces the fertilizing power of sperm without reducing its oxygen consumption appreciably, and produces, when injected into rabbits, an antiserum which agglutinates sperm (33). Results obtained by activation of unfertilized marine eggs with bivalent cations seem to favor a colloidal chemical as against the permeability theory of egg activation (34).

METABOLISM OF DEVELOPMENT

Tyler (35) gives an excellent theoretical discussion of the energy requirements in development, preceded by a discussion of the

dissociability of fundamental processes such as growth and differentiation.

Respiration.—The question of differences in oxygen consumption of different parts of the amphibian gastrula which is important in connection with the organizer problem has been reinvestigated. Barth (36) and Boell (37) eliminated one major source of error in previous work by taking into consideration local differences in amount of inert yolk. In both series of experiments, using different techniques, a gradient in the rate of oxygen consumption of what may be considered as "active material" was demonstrated, with its peak at the animal pole and the lowest value in the vegetal pole. The dorsal blastopore lip (organizer) is only slightly lower than the animal pole but higher than a corresponding equatorial region on the ventral side which indicates a second dorsoventral gradient. It remains to be seen whether this metabolic pattern has a causal relation to the concomitant morphogenetic events. In this respect it is of considerable interest that Philips (38), using the Cartesian Diver technique, finds no significant difference in oxygen consumption of different regions of the chick blastoderm in the head process stage; that is, at a time when many morphogenetic processes go on. In sea urchin development, the extensive work of the Scandinavian school has brought us closer to a correlation of specific morphogenetic processes with specific metabolic processes. Recent progress in this field is admirably reviewed by Lindahl (39).

Child (40) continues his studies of gradient patterns of oxygen consumption in intact embryos using vital dyes. The oxygen consumption of entire embryos and larvae of the salamanders *Amblystoma punctatum* and *tigrinum* (41), of *Petromyzon* (42), of chick embryos in the shell, and of differentiated tissues of chick embryos (43) were measured.

Enzymes.—It is evident that for the correlation of structural differentiation with chemodifferentiation a study of localized enzyme action during embryogenesis is of primary importance. The gradual differentiation of cholinesterase was determined in grasshopper (44) and in amphibian development (45). The building up of this enzyme is synchronous with the differentiation of the nerve cells in the former and with the development of functional activity in the latter; in fact, a causal relation between enzyme activity and attainment of swimming activity in salamanders is

strongly suggested. Acetylcholine was found localized in the brain of the six-day chick embryo, and from this stage it increases progressively (46). Moog (47) discovered interesting changes in the alkaline and acid phosphatase contents of the nervous system of young chick embryos, starting with an even distribution at one day and followed by concentration in some regions and disappearance in others. Bodine & Allen (48) give additional data of protyrosinase in the grasshopper egg and demonstrate its presence in the intact embryo. Two lipolytic enzymes were found in the yolk of the same egg (49). Pickford (50) makes a careful quantitative analysis of the peptidase activity of different regions of the early amphibian gastrula. Cytochrome oxidase appears in the chick embryo on the fourth day (51) together with cytochrome-*c* (52). The niacine content of the chick embryo, very low up to eleven days of incubation, rises sharply from then on up to hatching (53). Barnett & Bourne (54) give a detailed account of the highly specific distribution of ascorbic acid in different tissues of the chick embryo during the entire incubation period. An active role in histogenetic differentiations, particularly of skeletal tissues, is strongly suggested.

Dietary factors.—An exclusive diet of worms in the salamander *Pleurodeles* resulted in severe hind limb malformations (55). Spinach feeding in tadpoles resulted in heavy deposition of calcium oxalate kidney stones (56). Warkany and collaborators have studied in detail the effects of a vitamin D-containing rachitogenic diet fed to the mother on the skeletogenesis in rats (57, 58).

Miscellaneous.—The rate of cleavage is accelerated in dense populations of sea urchin eggs. An alcohol-soluble agent extracted from eggs (59), as well as hypotonic sea water (60), and copper (61) were found to have such an effect, whereas carbon dioxide slows down the rate of cleavage (62). The photodynamic action of dyes, particularly neutral red, on sea urchin eggs was investigated (63). The glycogen content of *Rana pipiens* embryos shows a peak at neurulation and decreases steadily up to hatching (64). Data on density and weight of grasshopper embryos are given by Bodine & Robbie (65). Of considerable physiological interest are Copenhaver's (66) experiments on extirpation of liver primordia in early salamander embryos. Hepatectomized embryos develop a fatal anemia one week after yolk resorption. Heterotopic liver transplantation prolongs survival, but feeding and injection of liver have no effect. The symptoms are ascribed to the lack of a liver-

produced substance which is essential for erythropoiesis in other organs.

EXPERIMENTAL MORPHOGENESIS

Early localization.—Pasteels (67) has revised Vogt's classical maps of the prospective organ-forming areas in early urodele and anuran gastrulae, using the vital staining method. Such topographic maps are the basis for experimental work but not indicative of a preformed organization, or of inherent potencies of germ areas. Only isolation or similar experiments can give information concerning the latter. Spratt (68), using the technique of plasma-clot culture, has demonstrated a segregation of definite organ primordia in very early stages of the chick blastoderm. Different levels of the neural tube as well as the notocord are prelocalized in the pre- and early primitive streak stages. His observations suggest a modification of our concept of the origin of the primitive streak; it originates by local growth *in situ* rather than by forward growth of posterior blastoderm material. Rawles (69) finds that in the slightly later head-process stage the heart-forming potencies are distributed in two lateral areas which are more extensive than the actual heart-forming regions and which have radial gradients. They represent excellent examples of "morphogenetic fields." The angle between the axis of the chick embryo and the longitudinal axis of the shell, as well as the turning of the embryo to one side are not as stable as had been thought before; they may undergo changes during development (70). It has now been demonstrated experimentally that the mammalian egg conforms with other vertebrate eggs in that it has a labile organization which makes regulation and twinning possible. Nicholas & Hall (71) reported producing two rat embryos from one egg, and one embryo by fusion of two eggs. The kidney capsule was found to be a particularly favorable site for the growth and differentiation of rat primordia (72).

Embryonic induction.—While in an earlier period of experimental embryology inductions were considered as specific responses of embryonic tissues to specific stimuli, it becomes apparent that the situation is more complex. For example, in the classic case of lens induction the optic vesicle is by no means irreplaceable as a lens inductor. It appears that differentiations such as lens formation are called forth by the synergetic action of a series of more or less nonspecific factors which may even substitute for each other. This concept is brought out again in the careful analysis of

lens formation in *Rana pipiens* by Liedke (73). Head mesoderm plays an important role in that it "conditions" overlying ectoderm to become responsive (competent) to the optic vesicle stimulus and is even capable of inducing lentoids. They appeared in explants which contained head mesoderm and ectoderm but no optic cup. Moreover, many differentiations can be called forth in indifferent embryonic tissue by agents which seem to be liberated by any number of structures and which are certainly not the "normal" inductors. For instance, Harris (74) obtains neural and cartilage differentiations from prospective epidermis of the early gastrula transplanted into tadpole tail musculature. Likewise, the excellent differentiation of lenses in the absence of the optic cup, of nose, horny teeth, etc., which Emerson (75) finds in transplants of late gastrula ectoderm to the tail regeneration blastema of tadpoles must be attributed in part to the complex agents prevailing at this site, which is nothing less than an indifferent medium, as the author claims. Nervous tissue may substitute for the Wolffian duct as an "inductor" of nephrogenic tissue (76). The posterior part of the notocord can "induce" head structures (77). It may also be possible to explain along these lines the seemingly paradoxical results of Bodenstein (78) who finds that prospective balancer area from a neurula will form balancer when grafted over old somites, but is "induced" to form neural masses when grafted over young somites. On the other hand, Spemann (79) reported in a posthumous paper that the adult liver does not exert an inductive influence on an implanted piece of undetermined gastrula ectoderm as he had expected; the latter, instead of being assimilated, calls forth sarcoma-like growth and destruction in its surroundings.

Some instances of more specific inductions may be mentioned. After the destruction of the prospective lens material in the neurula several substitute lenses may be formed simultaneously out of upper iris, retina, and overlying epidermis (80). *Triturus torosus* larvae show excellent Wolffian lens regeneration from the upper iris (81) whereas optic cups of the teleost *Fundulus* show no signs of lens induction or regenerative capacity (82). The nasal sac can differentiate independently of the telencephalon (75, 83) but the mesectoderm surrounding it is necessary for its complete differentiation (83). The pars intermedia of the hypophysis is induced by the diencephalic floor (84); but in later stages its growth and activity are inhibited by the hypophyseal hypothalamic nerve trunk (85).

The different regions of the anuran gastrula are not as independent of each other with respect to their gastrulation movements as had been thought before (86). In insects (Neuroptera) the differentiation of ganglia and of the ectodermal parts of the extremities is independent of the mesoderm to a considerable degree (87).

Despite its complexity, the regenerating feather germ is ideal for the study of basic problems of experimental embryology. F. R. Lillie and co-workers have analyzed this system in a series of outstanding papers which are lucidly reviewed by Lillie (88). The papilla of the germ represents an organizing center whose properties are strikingly similar to that of the amphibian organizer. A recent study (89) reports on the production of chimeric feathers, composed of parts of breast and saddle feathers, and the mutual correlation between the components.

External agents.—The rather specific morphogenetic effects of lithium salts which produce microcephaly and cyclopia in Amphibians were reinvestigated in the frog by Hall (90), using the explantation method. Calcium and potassium ions have a protective effect. The experiments give additional support to the contention by previous workers that the primary action of lithium is on the organizer. Töndury (91) finds disturbances of mesoderm and medullary plate formation in salamander embryos reared in testosterone, and serious damage to the mitotic mechanism in embryos reared in estradiol. Striking unilateral effects in the former experiment remain unexplained. Rulon (92) studied the morphogenetic effect of pilocarpine on sea urchin development. Ryan (93) made the theoretically interesting observation that the time-temperature relation during cleavage of amphibians differs significantly from that of later stages. Moore (94) studied the differences in temperature tolerance and time-temperature relations of five species of frogs. Supranormal temperatures may increase the relative length of the head without changing total length (95).

Melanophores.—The review of DuShane (96) gives a critical account of the extensive work done in recent years on origin, migration, and color pattern formation of the amphibian and bird melanophores. The reviews of Lillie (88) and Willier (97) contain chapters on the developmental mechanics of feather pigmentation. Of recent contributions, the thorough study of Watterson (98) deserves mention. He traces the migration of the melanoblasts from

deeper layers into the epidermis to unexpectedly early stages and demonstrates a rapid postmigratory proliferation which is unusual for differentiated cells. The active part played by the feather cells themselves in the process of pigmentation is emphasized. For the first time the origin and pattern formation of the eye pigmentation in urodeles was subjected to an extensive analysis by Barden (99). Melanophores as well as guanophores and xanthophores originate in the neural crest. The pigment pattern in the iris is controlled by factors located in the iris. A special investigation is devoted to the darkening of the iris at metamorphosis which is controlled in part by a diffusible substance originating in the eye. Xenoplastic transplantations between European *Anura* and *Urodela* show that the pigment pattern formation in the skin of the trunk is, at least in part, determined by subjacent tissues (100). Similar experiments on American forms indicate a more complex situation (101). The thalamus floor of urodeles was found to be a source of melanophores (102). Melanophores retain their capacity for rapid multiplication in tissue culture for a period up to six months (103).

REGENERATION

Invertebrates.—The analysis of regeneration in the coelenterate *Tubularia* is of particular interest because it is being pursued along physiological lines. Goldin & Barth (104) find that in fragments of coenosarc, when removed from the perisarc, morphological dedifferentiation and obliteration of polarity and of the respiratory gradient take place. Such a system offers a unique opportunity for the study of the origin of polarity and the role of external factors in regeneration. Polarization can be controlled by oxygen tension, but in the presence of an optimal oxygen tension the pH of the medium can be made the controlling factor for polarization and rate of regeneration (105). The theoretically significant point is thus established that oxygen is not a specific "hydranth inducing" agent, but one of many necessary conditions for regeneration. It is of significance that the effects of hydrogen-ion concentration and oxygen concentration are interrelated (106). Polarity is probably determined by differentials in the resultant of these two, and possibly by other factors. Only a small percentage of the overall oxygen consumption in a stem piece is required for, and involved in, regeneration (107). The so-called "regeneration unit," the in-

crease in mass per time unit (Barth), employed frequently in *Tubularia* regeneration, must be used with caution since growth in length and rate of regeneration vary independently of each other (108, 109). In annelids chloragogue cells furnish the nutritive material for both regeneration and egg formation. As a result of competition, sexual reproduction inhibits tail regeneration (110).

Vertebrates.—Nicholas & Oppenheimer (111) have studied experimentally the progressive decrease in regulative and regenerative properties of *Fundulus* (teleost) embryos and discussed the factors involved in this limitation and in the recurrence of regenerative power in certain organs of more advanced stages. They arrive at a fairly straight curve of progressive restriction of regulation from the two-cell stage to the motile embryo by estimating quantitatively the maximum amount of tissue that can be removed without interfering with reconstitution.

Limb regeneration in urodele amphibians can be prevented by x-radiation, denervation (see page 12), colchicine treatment (112), and neutron radiation (113). The latter agent is much more effective than x-radiation. The histological effects are correlated with dosage (113). New evidence is offered for the strictly local origin of blastema cells in regenerating amphibian limbs (114) and for the participation of dedifferentiated cells in blastema formation (115, 116). Under normal conditions limb regeneration in anurans is limited to larval stages. Schotté & Harland (117) demonstrate a proximodistal gradient in the loss of regenerative capacity of hind limbs of old tadpoles. Rose (118) finds that limited limb regeneration can be evoked even in young and adult frogs by daily baths in concentrated sodium chloride solution. Russian workers have paid considerable attention to the metabolic processes in limb regeneration of amphibians (119). Striganova (120) gives new quantitative data on the protein metabolism in the stump and the regenerate, which indicate that protein breakdown products in the former furnish material for the upbuilding of the blastema. Sokolova (121) tries to correlate the regenerative potency of adult tissues with their cathepsin contents, which latter enzyme is instrumental in the protein breakdown in the regeneration stump.

The tail bud of chick embryos of eleven to fourteen somites can be regenerated after its complete extirpation. In older stages, at least part of the primordium must be left intact in order to obtain regeneration (122).

NEUROEMBRYOLOGY

The differentiation of the central nervous system is to a considerable degree controlled by peripheral nonnervous structures. Bueker (123) finds a hypoplasia amounting to 75 to 90 per cent of the lumbosacral motor column of the chick following hind limb bud extirpation. In accordance with this, motor hyperplasia is found in genetically polydactylous fowl (124). A similar effect on motor neurons in urodeles had been contested. It seems now that the difference between chick and salamander embryos is not of a fundamental nature but only one of rate of reaction. Stultz (125) finds definite motor hyper- or hypoplasia following early limb bud transplantation or extirpation in salamander larvae which are allowed to develop to metamorphosis stages, whereas younger stages show only slight responses. Commissural neurons adjacent to motor neurons do not show a hypoplasia following limb extirpation, but rather what seems to be a compensatory hyperplasia (126). Spinal ganglia invariably had been found to react sensitively to peripheral changes both in amphibian and chick embryos. This statement can now be extended to include mammals, as shown by limb amputation experiments in rats (127) and a case of congenital absence of the limb in a human fetus (128). The hypothetical influence of outgrowing intracentral fiber tracts on the differentiation of neuroblasts which they pass on their way (Kappers-Bok) has always been a matter of controversy. Strong experimental evidence is now forthcoming against this idea. Bueker (123) finds that lumbosacral segments of the chick spinal cord, when isolated and reared in the embryonic coelom, develop full-sized motor columns provided limbs are attached to them. Rhines (129) finds that the structural pattern of the spinal cord underlying spontaneous motility in the early chick embryo differentiates normally if the myelencephalon is severed from the metencephalon. On the other hand, the decussation of Mauthner's fibers in fishes (130) and amphibians (131) seems to be dependent on the special structural configuration at the site of crossing. The embryonic medulla of *Amblystoma* retains its own growth rate but shows no tapering when transplanted to the brachial level of the cord (132).

It has been found generally that peripheral nonnervous structures do not require innervation for their morphogenetic and histological differentiation. This has been confirmed in several instances. Innervation and connection with brain centers is not

necessary for the differentiation of the sensory areas of the avian inner ear (133) nor for the differentiation of nasal epithelium (75, 83). Neither has eye extirpation any influence on growth rate and gonad development in amphibians (134). The differentiation of muscle fibers in nerveless chicken limb transplants proceeds normally to the stage of perfect cross striation, but nerve supply is necessary for their continued growth and structural maintenance (135). On the other hand, there is no doubt that the regeneration process in higher forms requires innervation. The regeneration of salamander limbs is strictly dependent on nerve supply at the amputation level. However, the question has not been settled which one of the components of peripheral nerves is effective. Singer (136) in a careful reinvestigation based on histological checks superior to those of earlier workers discounts an influence of the sympathetic fibers and claims a significant role for sensory fibers. He makes the interesting suggestion that the problem may resolve itself to one of quantitative minimum requirements rather than one of specific qualitative requisites. The limb regeneration in anurans which is limited to tadpole stages (see page 10) depends likewise on the presence of nerves at the cut surface (137). The mechanism of the nerve action involved is still obscure, but the analysis of this problem has been carried a step further. As is known, blastema formation is preceded by a process of dedifferentiation of tissues at the amputated surface. In denervated stumps, dedifferentiation will go on unchecked, but can be checked by transplanting a young blastema onto the denervated stump (138). This implies that the nerve supply somehow maintains a proper balance between the two antagonistic forces, dedifferentiation and blastema-formation.

Nerve pattern formation.—A stimulating review of the problems involved in nerve growth and nerve pattern formation is given by Weiss (139). He emphasizes the physicochemical conditions underlying the first outgrowth of pioneer fibers and their subsequent reinforcement (fasciculation) and branching. The final phase of pattern formation he considers as a process of "towing" in which the organ primordia, while they grow out, carry the previously anchored fibers along. This latter concept may require revision in view of new observations of Piatt (140). This author first obtains entirely nerveless differentiated limbs in salamanders by very early extirpation of the limb level of the spinal cord, and then transplants these limbs near a source of outgrowing fibers in an-

other larva. The invading fibers form a nearly normal pattern in the full-differentiated transplants demonstrating that they are more active in pattern formation than the "towing" concept would imply.

Development of reflexes.—In a posthumous paper by Coghill (141) the interesting discovery is reported of a pronounced periodicity in the development of skin sensitivity to light touch in *Amblystoma* embryos. The periodicity is endogenous and not attributed to fatigue. Sawyer (45) established a close correlation between cholinesterase development and development of early reflexes in *Amblystoma* embryos. He found a sharp rise in the former in the stages when the swimming reflexes begin. The development of the corneal reflex in metamorphosing amphibians (eye-bulb retraction and lid closure) was studied by Kollros (142). The maturation of the brain center for this reflex is under the direct control of the thyroid hormone (142). Weiss (143), using this corneal reflex in salamanders, is able to demonstrate that exteroceptive sensory fibers can be conditioned or "modulated" by foreign peripheral structures to perform new specific responses. The same phenomenon had been demonstrated previously for proprioceptive and for motor fibers. Eyes were transplanted to atypical positions in the head. After sensory fibers which had previously innervated skin had grown into the transplant the corneal reflex could be elicited in the host eye by touching the cornea of the transplant eye.

Nerve regeneration.—War surgery has given a new incentive to the study of nerve regeneration. An admirable, up-to-date review of the field is given by Young (144), including recently published material by the author and his group at Oxford. The main emphasis of the review is on the histogenetic processes, but the question of functional nerve repair is duly stressed. The problem of creating optimal conditions for nerve outgrowth is, of course, of outstanding practical importance. In this respect Weiss (145) finds that the method of inserting the ends of a severed nerve in a closely fitting sleeve of living, or adequately preserved, artery is superior to suturing. This method reduces the chance of disorientation, neuroma formation, and bifurcation of fibers at the gap, which have been demonstrated again (146). Where larger gaps are to be filled, frozen-dried nerve material is recommended (147). Clark (148) in a carefully controlled series of experiments on rabbits, finds no evidence of regeneration capacity in the nerve fibers

of the brain. Injections of atropin, or feeding of biotin (149) or of vitamin E in the diet have no detectable effect on motor regeneration in rats (150), but biotin stimulates growth of nerve tissue in tissue culture (151). Vitamin B₁ has no effect on axon growth of embryonic spinal ganglia *in vitro* (152). The reinvestigation of the regeneration of the optic nerve in adult salamanders yielded important results. Stone & Farthing (153) have demonstrated that adult salamander (*Triturus viridescens*) eyes which have been extirpated and reimplanted to the same or another individual as many as four times can regain perfect function after each operation. The tests for return of vision were rigid and adequate. This is the more remarkable as the retina and lens degenerated, and subsequently regenerated in each instance. Of particular interest are the observations of Sperry (154) concerning the functional performance of eyes of newts which were rotated 180° and reimplanted. The visual perception was completely reverted and inversed, with no signs of functional adaptation. The perplexing problem of how the regenerating optic nerve fibers re-establish precisely their previous connections with their centers despite a random arrangement at the site of severance is ably discussed by the author, but not yet solved.

HORMONES IN VERTEBRATES

The sex hormones and their role in the determination of secondary sexual and other somatic characters are still in the center of interest. Few original contributions of importance have been published in the period under discussion but previous work in this field has been summarized and well integrated in several outstanding symposia. The introductions to two of them by Riddle (155) and Moore (156) deserve mention.

Mammals.—Burns (157) gives a penetrating analysis of experiments performed on the opossum by himself and by others. This marsupial is ideal material because the fetus is accessible to hormone injections when it enters the pouch at a very early stage of sex-differentiation. As in rodents, the gonads are refractory to any hormone influence but the secondary sex structures respond sensitively. A thorough knowledge of their normal development, together with a careful timing of the injections enable the author to interpret the observed effects in terms of two major groups of variables involved: specificity, concentration, and time of action

of the two heterologous hormones concerned, and the pattern of responsiveness inherent in the affected tissue. The latter changes from stage to stage and differs for the different structures. Of interest are observations on the relation of hormone concentration to response which indicate that the "paradoxical effect" of the stimulation of organs of one sex by hormones of the opposite sex may be correlated with the use of excessive doses. The important contributions of Greene and associates to the same problems using the method of injection into the pregnant female rat are reviewed by the senior author (158). The sex specific effects of both hormones are clearly brought out, as well as their mutually antagonistic action on sex differentiation: they nullify each other when injected in properly dosed combinations (159). Moore had previously raised doubts as to the validity of deducing from such injection experiments that in normal development the determination of secondary sex organs is under the hormonal control of the embryonic gonads. He finds his assertion confirmed in new experiments on the opossum (160) which indicate, though in an indirect way, that the gonads may not secrete hormones until in late stages when secondary sex differentiations are already under way. Furthermore, subcutaneous transplants of primordia of primary and secondary sex structures into young normal or castrated male or female rats failed to show any modifications by sex hormones of the host, nor was there any indication that the gonads included in the grafts had an effect on adjacent transplant structures (161).

The effects of sex hormones on the growth of the skeletal system are discussed in a review by Gardner & Pfeiffer (162). The influence of hormones on the skeletal development of the dog is considered in the extensive hybridization experiments of Stockard and others (163). The role of the thyroid gland on skull development in the rabbit (164) and that of the pituitary growth hormone on the skeleton of mice and guinea pigs (165) were investigated. The thyroid of the rat shows histological evidence of functional activity beginning on the nineteenth day (166).

Birds.—The influence of hormones on sex differentiation including plumage is reviewed by Danforth (167) and Willier (97). Transformation of the left testis into an ovotestis can be accomplished in the pigeon by a slight increase of estrogen in the blood of the mother (155, 168). Experimentally feminized chickens reverted gradually to the male condition several months after hatch-

ing (169). Thyroidectomy affects not only the coloration but also the structure of regenerating feathers (170). The functional activity of the melanophore-dispersing pituitary hormone was followed through embryonic and posthatching stages of the chick (171).

Amphibians.—The relation of sex hormones to differentiation was reviewed by Witschi (172) and the problem of sex inversion by Humphrey (173). In contrast to most higher vertebrates the gonad primordia of amphibians are so unstable that a complete inversion of the genetic sex can be accomplished. Complete masculinization in tadpoles was obtained by rearing them in low concentrations of testosterone (174) or in pregnenolone (175). The same result was obtained in the axolotl by substituting an embryonic testis for an ovary primordium whereby the unoperated host gonad is transformed into a functional testis (173, 176). For the first time offspring were obtained from one such male (177); their sex ratio shows rather conclusively that in the axolotl the female sex is heterogametic. Humphrey (178), in heteroplastic transplantation experiments involving combinations of gonad primordia of different sizes in the same individual, finds further evidence for the growth-inhibitory action of one (the larger) gonad on another gonad of the same sex. Witschi (172) offers a tentative explanation of this phenomenon; he considers it the result of competition for a gonad growth promoting substance.

Fishes.—In poeciliid fishes, testosterone has a masculinizing effect on the gonopodium, an anal fin modified into a copulatory organ (179, 180).

HORMONES IN INVERTEBRATES

The remarkable progress made in recent years in the analysis of hormones controlling developmental processes in insects has been reviewed by Bodenstein (181). In addition to metamorphosis and molting hormones, substances which control egg formation and regeneration are known. The corpus allatum is the most important organ of internal secretion. The assumption that the ring gland of the larvae of Diptera is homologous to the corpus allatum and the corpora cardiaca of the adult is confirmed (182). Considerable progress has been made in the unification of the rather complex picture of the activities of the ring gland. Secretions of this gland control the growth of larval organs, of imaginal differentiation, and of metamorphic changes (183, 184) as well as egg pro-

duction in the adult (185). The growth and differentiation hormone is produced throughout larval life in increasing quantities. Concurrent with these quantitative changes are changes in the sensitivity and type of response of the affected primordia (183, 184). In principle, the situation resembles that found in the opossum (page 14). Vogt (185) in a series of brilliant experiments demonstrates a species specificity of the ovary-growth stimulating ("gonadotropic") ring gland hormone of different species of *Drosophila*. Day (186) finds in muscoid Diptera that the effects of extirpation of the corpus allatum are not limited to the ovaries but extend to fat bodies and oenocytes, a fact indicating a general metabolic rather than a specific effect on gonads. In Lepidoptera the situation seems to be different from that found in Diptera. Piepho (187), in an extensive series of experiments, finds that in moths a hormone produced by the corpora allata stimulates molting in larval stages but that the pupation reaction of the hypodermis is called forth by another hormone produced in the brain or in the prothorax gland. An antagonism exists between both hormones (the corpus allatum hormone inhibits pupation), and a gradual shift in the relative concentration of both apparently accounts for the normal sequence of events. The chemistry of eye color hormones is competently reviewed by Ephrussi (188). A hormone controlling molting and imaginal differentiation is now reported for Hymenoptera (189). In crustaceans the sinus gland adjacent to the eye stalk has long been known to produce a chromatophore-controlling hormone. This gland in addition seems to control molting and certain metabolic changes associated with this process (190).

DEVELOPMENTAL GENETICS

An intimate knowledge of the mechanisms by which genes influence and "determine" developmental processes is a prerequisite for a full understanding of both the process of heredity and the process of development. Consequently, both geneticists and embryologists participate actively in elucidating the problems involved.

Nucleus and cytoplasm.—Fankhauser and co-workers (191 to 195) and Costello (196) extend to a number of urodele species their studies of cold- and heat-induced polyploidy and haploidy. The high mortality of androgenetic salamander eggs is correlated with abnormal mitosis (197). Maternal inheritance was found in species

hybrids of sea urchins (198) and in the inheritance of the number of lumbar vertebrae in the mouse (199). The important studies of Haemmerling on nuclear-produced morphogenetic substances in the alga *Acetabularia* are continued (200).

Morphogenetic analysis.—Gene action in development is being studied with the methods of experimental embryology in an attempt to establish the seat of "primary" or "local" gene action and the role of embryonic inductions in the fading of secondary gene effects. Several reviews deal with the developmental mechanics of individual genes in the mouse (201), of the creeper factor in fowl (202), of the frizzle factor in fowl (203), and of gene-controlled color patterns in amphibians (204) and butterflies and moths (205, 206). The physiology of eye-color genes in *Drosophila* is reviewed by Ephrussi (188). Much valuable information concerning the mouse may be found in the monograph of Grüneberg (207).

The first step in a morphogenetic analysis of gene action is to trace the phenotypic manifestations to early developmental stages, when they first become visible. Such studies offer occasionally a clue to the mode of gene action. Hereditary absence of the tail of the chick ("rumpless") can be traced back to the degeneration of primordial tail-bud tissue (208). The same abnormality can be copied by shaking of eggs prior to incubation (209). A new "tailless" mutation in the mouse which also affects the kidney seems to operate by way of circulatory disturbances (210). Another gene for taillessness in the mouse operates by resorption of an initially-formed tail (201). It is of interest to see that the same phenotypic manifestation can be produced by four different embryological mechanisms, which shows the complexity of the problem of gene action and the difficulties in arriving at generalizations. The first manifestations of the homozygous creeper factor in the chick have been traced back to early stages (211). Familial differences in the number of ribs in the rabbit are anticipated in very early differences in the pattern of ossification (212). A hereditary anemia in the mouse is due to an incomplete hemoglobin synthesis in the liver during fetal life; it subsides when bone marrow takes over the erythropoietic function after birth (213).

In view of the manifold interactions between parts of the developing embryo it is to be expected that gene-controlled developmental disturbances in one primordium may be transmitted to adjacent structures by means of inductions and similar mecha-

nisms. A clearcut case of such "indirect" gene effects was found in the creeper chick (214). The eyes of homozygous creeper embryos show severe abnormalities (coloboma, etc.). If their primordia are transplanted to the eye region of a normal embryo, they develop normally despite their genetic constitution. This shows that the creeper factor, in producing eye abnormalities, must act through agents extrinsic to the eye. Similarly, the "bar" and "eyeless-2" factors in *Drosophila* cause a reduction in the number of eye facets. The concomitant size reduction in the optic nerve centers (glomeruli) is not caused by direct gene action on the latter but indirectly, by an eye-glomerulus correlation via the optic nerve fibers (215).

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DEPARTMENT OF ZOÖLOGY
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GROWTH

NEOPLASTIC GROWTH

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Inquiry into the genesis of pathological processes has been a standard and profitable procedure of physiologists. As regards forces leading to new growth, the line of separation between physiological and pathological is often ill-defined. Some neoplasms are an inevitable consequence of long-continued physiological stimuli. It is not even certain that the milk factor that is carried in seemingly normal individuals for generations is a strictly pathological agent.

This review surveys only recent studies, and the limitations imposed upon us by the war render it even more incomplete. Limitations in space necessitate omitting a detailed consideration of special chemical and metabolic aspects of new growth which are broad enough to be subjects of later independent reviews. A *Symposium on Respiratory Enzymes* (1) includes discussions of tumor respiration. The chemistry of carcinogenic substances has been reviewed by Hartwell (2), Badger *et al.* (3), and Fieser (4). Enzymology of neoplasms has been thoroughly reviewed by Greenstein (5). Two books have appeared on the chemical aspects of new growth, *Biochemie der Tumoren* (6) and *Biochemistry of Malignant Tumors* (7). Other phenomena of new growth omitted here are covered in the new edition of Thompson *On Growth and Form* (8) and in Needham's *Biochemistry and Morphogenesis* (9). Vivid interpretations of fundamental problems of cancer include Overling's *Le Problème du Cancer* (10), and the reviews of Rous (11, 12) and Murphy (13).

CAUSAL FACTORS IN EVOLUTION OF NEW GROWTH

There are many factors contributing to the origin of new growth. They often act in unison or in succession so that it may remain doubtful which is the immediate cause of the new growth. Before considering the complexities of induction and maintenance of neoplastic growth some of these factors are considered separately.

Hereditary influences.—These may be the nearest direct cause of cancer; they are an ever-present influence accentuating or restraining or otherwise modifying other stimuli. They are not as easily defined as thought previously, as the history of the milk factor illustrates. Opinions on the role of heredity in the formation of mammary gland tumors differ. Some data (14) are in accord with the assumption that susceptibility is inherited as a single factor, while other data (15) are interpreted as indicating that the hereditary influence is negligible, the main factor being the milk factor. Differences in the incidence of breast tumors in virgin and in bred females of different strains are interpreted by assuming that the genetic background determines the amount of estrogenic hormones secreted or the rate of their destruction or the threshold sensitivity of organs to them (16, 17). The male parent is doubtless influential (18), a fact suggesting again a genetic influence. The latter may determine the response of mammary glands, not only to estrogenic stimuli (19) but also to the milk factor (20); it plays no role in the production of another estrogen-stimulated growth, that of the cervix (21).

In crossings of highly inbred strains with known genetic liability, it is not possible to predict the degree of susceptibility of the resultant hybrids (22). Cross breeding of two low tumor strains may produce hybrids with high susceptibility to tumors (22). Hybridization of a high leukemia strain with one low leukemia strain inhibits the incidence of this neoplasm, while another low leukemia strain does not (23). The genetic factors of leukemia vary with different strains (24). Susceptibility to spontaneous leukemia is inherited, probably as a multiple factor characteristic, and is influenced by undetermined environmental factors. In the hybrids the common logarithm of the per cent of leukemia is a simple function of the percentage of heredity from the high leukemia stock (24).

Strain-limited response leading to neoplasia has also been established for tumor-like growth of chromophobe cells of the pituitary (25) and for the Leydig cells of the testes (26). Little (27) has surveyed the genetics of spontaneous neoplasms in animals. At present it is wise to speak merely of strain characteristics and not of genetic characters, as the discovery of milk factor shows. Procedures now being adopted consist of: (a) the use of inbred lines, (b) foster-nursing members of these, following surgical re-

removal of fetuses immediately before delivery, and (c) transfer of fertilized ova to uteri of mice of other inbred lines (28) in order to determine the magnitude of an additional uterine influence. It is well to remember that inbreeding is a relative term, and that inbred stocks are not analogous to pure chemicals, since like all living matter they are subject to unpredictable modifications. Furthermore, some agents on the borderline of pathogenicity yet influential in the origin of new growth may pass to successive generations or may be present in the excreta of apparently healthy animals and affect others.

Genetic factors in the causation of human neoplasms are indicated by statistical data on identical twins. Of those analyzed (29), 94.7 per cent had the same type of tumor in the same organ, while the corresponding figure for dizygotic twins was 46.6 per cent. The fact that in 5.3 per cent of cases only one monozygotic twin was affected may indicate the role of some extrinsic force. Under experimental conditions a far greater modification of hereditary neoplastic tendencies can be demonstrated (see hormonal and nutritional factors). Even hereditary neoplasms may not eventuate in the absence of physiological quantities of hormonal or other stimuli; but it is also possible that certain cells are so constituted that they will become neoplastic at a given age, as in abirotrophy.

Embryonal disturbances; teratoma; analogy between organizers and carcinogens.—There is some recent confirmation (30) of earlier ideas that misplaced or abnormally retained cells or organs are particularly susceptible to neoplastic growth even though certain neoplasms formerly attributed to an embryonal disturbance, e.g. teratomas, can be induced by injection of zinc chloride into the gonad (9). Different mechanisms might reasonably explain other teratomas, such as abortive parthenogenesis or inclusion of isolated blastomeres (31) or of unspecialized cells (32). The incidence of twinning is high in families with ovarian dermoid or childhood teratomas. Both may involve common factors of heredity (31). Teratomas are a link between a developmental disturbance and a new growth. Nonovarian teratomas must be regarded as neoplasms, otherwise they would be resorbed, like normal tissues in ectopic sites (32). Some tumors in *Drosophila* arise in embryonic rests latent in the wall of the digestive tract. Some of the rests give rise to benign encapsulated growths, others to tumors lethal to one-half of the males (33). The old observations of Witschi that

if eggs of the frog became over-ripe before fertilization, abnormal growths would develop has been reinvestigated (34). These cauliflower-like, nodular, or papillomatous growths (34) are derived from uninjured cells that continue to divide at the normal rate. When such "tumors" are grafted into equivalent embryos they are usually slowly absorbed as grafts of normal tissue and survive only when the vitality of the hosts is weak (34). Similar growth abnormalities can be produced by treatment of frog eggs with chemical, physical, and other agents (35). They are not true neoplasms but may be more liable to neoplastic changes than normal tissue.

Neoplastic growth is regarded by many investigators as an escape from the organism's controlling individuation field with consequent abnormal differentiation and proliferation over and above normal (9). In a posthumously published study, Spemann (36) investigated whether the adult organism possesses determination fields. He implanted pieces from early amphibian gastrula, consisting of presumptive epidermis, between liver and abdominal wall so as to be connected with the liver and exposed to its inductive effects. Tumor-like growths arose, the character of which has not been analyzed by transplantation and other tests.

The idea that carcinogenesis by chicken tumor agents is analogous to the phenomena of organizers has been considered (37). Needham (9) assumes that neural plate induction like virus tumors could be propagated by appropriate cell-free evocators indefinitely. The synthesis of further supplies of evocator is stimulated autocatalytically.

Experiments undertaken to find out if carcinogens would act as evocators are contradictory, but this can be explained by differences in the methods used. Neural tube induction was obtained in isolated presumptive epidermis from *Amblystoma mexicanum* cultured in the presence of dibenzanthracene (38), while with developing ova of *Rana pipiens* only degeneration of a uniform pattern was noted (39). This was attributed to the carcinogenicity of the compounds tested. The amount needed to produce neural tube induction (38) was so minute as to suggest a direct action, while Woerderman as cited by Briggs & Briggs (39) suggested that carcinogenic hydrocarbon induced release of an organizer. Figure 138 of Needham (9) gives a visual picture of the interrelationship of carcinogenic, estrogenic, and evocator effects of different compounds. Thus both viruses and carcinogenic chemicals have been

compared with organizers, the former reproducing their kind as do autocatalysts, the latter not. The affected cells differentiate in an abnormal direction and continue to reproduce the new cell type. Embryonal cells have a broad competence and may in a strange environment grow into tumors under the influences of forces of these environments. Yet true neoplasms are rare in embryos.

Chromosomal disturbance; the mutation theory.—It is an axiom of developmental mechanics that all cells of a complex organism have the same chromosomal make-up, and that differentiation is not accompanied by a chromosomal change (40). If the neoplastic change is accompanied by chromosomal alteration, it constitutes a mutation, and since the change affects only somatic cells and not the germ plasm the mutation is of the somatic type.

Neoplastic cells contain many chromosomal disturbances (41); are these expressions of the abnormal state or its cause? Endomitosis or division of chromosomes within the nucleus without breakdown of nuclear wall, followed by doubling of nuclear volume and cell size, is common in neoplastic cells and successive endomitoses lead to intricate chromosomal patterns. Diploid and polytene chromosomes are common with sequelae of greater nuclear volume, increased number of nucleoli, and larger size of chromosomes. Polytene chromosomes may occur in nonmalignant tissues (41). Chromosomal reallocations in maize may result in permanent alterations involving growth (42). Numerous different agents, including viruses, can produce inherited tendencies by increasing the frequency of chromosomal breaks and relocations or by altering the growth-regulating regions of the chromosomes (42). Carcinogens produce abnormal mitoses *in vitro* by splitting off chromosomes (43). If cancer does arise by mutation, this is likely to be a structural chromosomal change or gene mutation (44).

Some agents that are powerful in producing mutations are also powerful as carcinogens, e.g., ultraviolet light and x-rays, although the ability of chemical carcinogens to produce mutations of the usual kind has not been demonstrated. X-irradiation of *Arbacia* eggs results in unequal distribution of genic material resulting in viable daughter cells with altered characteristics; induction of cancer probably involves similar changes in the hereditary complex of cells (45). The frequency of genetic mutations bears a simple linear relationship to the dose administered (46), being an exponential function of the dose. Thus the theory of genetic muta-

tion of x-rays is susceptible to experimental tests. Genetic mutation may initiate a permanent alteration in the nucleic acid metabolism resulting in neoplastic cells (47). It will be necessary to determine whether the spectrum for carcinogenesis corresponds precisely to the absorption spectrum of nucleic acid (44).

When *Paramecia* were subjected to different carcinogenic agents, abnormal cells appeared which on further propagation in absence of these agents yielded populations of cells varying from normal to monstrous forms (48). It is doubtful whether these changes are comparable to neoplasms. Earle (49) noted morphological changes suggestive of neoplasia in tissue cultures to which minute amounts of methylcholanthrene were added. When injected into animals these cultures produced sarcoma. However, similar changes were noted in the control cultures. This neoplastic transformation *in vitro*, whether spontaneous or induced, can be regarded as a mutation. "Spontaneous" mutations undoubtedly have their causative forces. Metabolites that accumulate in tissue cultures are removed intermittently and incompletely, and the nutrient itself is an unknown and variable complex.

A permanent modification resembling a mutation can also be produced in tumor cells by radiation. This manifests itself by changes in transplantability (50). The conditions under which this occurs correspond to those that produce mutations in *Drosophila*. The malignant, irreversible changes occurring in the course of transplantation in certain benign tumors, fibroadenoma of the breast (51) and pulmonary adenoma (52), may likewise be interpreted as mutations.

It is generally assumed that the success of transplantation depends on the genetic relation between host and transplanted cells. If so, transplantation experiments are suitable to disclose genetic relationships. Normal splenic grafts follow a well defined pattern. Cells from induced leukemia and tumor may differ from those of their hosts and may also differ greatly among themselves (53).

Historical aspects of the numerous objections to the mutation theory of neoplasia have been cited elsewhere (53). This theory will not become a fact until alterations in the genes coincident with the malignant change are demonstrated.

Carcinogenic chemicals.—In a recent survey Hartwell (2) lists 697 compounds that had been adequately tested, of which 192 had produced neoplasms. Carcinogenic chemicals are found in a great

variety of chemical classes, and their structure varies widely; only fragmentary correlation can be made between molecular structure and carcinogenic activity (2). Slight changes in the configuration of the compounds result in profound changes in carcinogenicity (3, 4, 54). There is evidence for organ selectivity of some compounds and of pluripotentiality of others. Data of different investigators are not strictly comparable; the variables include: genetic constitution of the animal, its age, sex, diet, physical condition, purity of the compound, the dose, the physical state of the chemical, the site of its administration, and the solvent or vehicle used in applying it (2). There is a straight line relationship between average latent period and logarithm of the injected dose (55). The smallest amount of benzo[a]pyrene that produces sarcoma is in the neighborhood of 4 μ g. (55); the amount of chemical actually influential in producing the neoplastic change is probably only a fraction of this. A single cutaneous application of methylcholanthrene can produce tumors (56). The period of latency may be as long as one-third of the life span of the animal. The primary change is damage to the epithelial cells followed by repair and hyperplasia. The regenerated cells are more resistant to the agent than normal epithelial cells. The tumors originate in such altered cells long after the chemical agent is nondemonstrable by the usual chemical tests (56). Carcinogenesis is not mere stimulation of growth (57), as indicated by the long period of latency. Carcinogens are not growth stimulants *in vitro* (57). When applied to young rats they may produce dwarfing (58), but with removal of the carcinogen growth is resumed. The specific affinity of azo compounds for the liver, of aniline dyes for the bladder, of estrogens for the breast, etc. may be in part the consequence of a specific accumulation of these compounds in the respective organs due to specific affinities. The fact that nonsteroid estrogens produce carcinoma of the breast as well as steroid estrogens may indicate that they act by inducing a physiological state in which breast cells are susceptible to other carcinogenic stimuli. Often the relation of the chemical to the cells stimulated is unknown. This is true for leukemia, which can be readily produced by carcinogenic chemicals (59) or estrogens (60). The pluripotentiality of some compounds can be explained by their dissemination in the body and by wide affinities. Sometimes special procedures are necessary to demonstrate pluripotentiality because the first neoplasm produced

destroys the animal, e.g., to produce leukemia by methylcholanthrene the chemical is painted in small concentrations on different parts of the skin (59); to demonstrate the ability of estrogens to produce carcinoma of the cervix uteri, it is necessary to remove the breast cancers which appear earlier (61). The sequence of events in carcinogenesis is explained by assuming that the action of the chemicals is indirect, resulting in the release of another substance directly responsible for the neoplastic change (62). This has also been assumed to be true for the action of organizers. According to another plausible theory, cells so stimulated are excellent hosts for carcinogenic viruses (11).

The injected chemical may disappear long before the onset of neoplasia, as indicated by absorption spectrum analysis (63). A considerable local storage may take place in vesicles near the site of injection (64). When benzpyrene with violet fluorescence is painted on mouse skin, it is transformed locally into a derivative with blue fluorescence (65); this can be detected six hours after painting and persists for several weeks. It is confined mainly to quickly proliferating cells of the malpighian layer and is excreted along with other derivatives (65, 66). Irradiation with ultraviolet light results in the liberation of hydrogen peroxide and in the formation of a derivative which inhibits urease. Freshly prepared benzpyrene is not toxic to urease. This may explain the photolethal effect of some hydrocarbons (67), but light does not seem to play a part in the carcinogenesis by hydrocarbons.

Carcinogens profoundly alter the metabolism, enzymatic process, vitamin storage, and other activities of normal cells, and numerous data have been gathered, in the hope that knowledge concerning these will shed light on the mechanism of carcinogenesis. Azo dyes and their split products inhibit several enzyme systems (5, 68, 69, 70). Administration of dibenzanthracene to rats results in decrease of vitamin A in the liver (71). After exposure to methylcholanthrene for several generations *Paramecia* survive partial starvation longer than normal *Paramecia* (72).

Nutritional factors.—Restriction of food intake inhibits profoundly both the development of tumors and tumor growth, and it is possible that many chemical inhibitors act indirectly by producing malnutrition. Tumors in underfed animals appear at a later age (73). Addition of vitamins or minerals to an otherwise restricted diet does not alter the tumor incidence. Formation of

breast tumors can probably be inhibited by caloric restriction any time before the tumors begin to appear. In the experiments of Visscher *et al.* (74) no tumor occurred in the underfed animals, while the incidence in the controls was 67 per cent. Thus even the milk factor can not induce tumors in animals that are underfed. Under similar conditions the incidence of spontaneous leukemia is markedly lowered in a high leukemia stock of mice (75). Underfeeding restricts the nutritive supply, metabolism, and growth of tissues. Initiation of tumor may occur, but there is a lack of that energy required for the "eventuation" of tumors (73). Bioassays made to detect malignant lymphoid cells in underfed mice failed to reveal their presence at a time when their normally fed siblings had died of new growth, but disclosed them in older underfed animals (75). The decrease in the incidence of breast tumors may be due to a diminution of hormonal stimuli, as indicated by underdevelopment of mammary glands and ovaries and by sterility (73, 74). Caloric restriction retards growth, markedly increases the longevity of the animals, and decreases the incidence of spontaneous neoplasms to which the animals are susceptible and of certain nonneoplastic diseases (76, 77). Lymphoid tissues are atrophic in the underfed animals, and this may explain the scarcity of respiratory diseases (77). High fat diet increases the incidence of spontaneous breast tumor and that of epithelial tumors of the skin induced by ultraviolet light or benzpyrene and shortens their incubation period (78, 79). The incidence of lung tumors and of sarcoma is, however, unaffected (78). The growth promoting activity of the fat resides in the fatty acid fraction; it is increased by heating fat to 300°C. (79). Cholesterol heated to 150°C. is carcinogenic (80). High cystine diet facilitates induction of leukemia by methylcholanthrene and also protects the animal against arteriosclerosis produced by methylcholanthrene (81). Mice on low cystine diet failed to develop mammary gland tumors (82). Low protein diet favors the induction of neurofibromas by ergot (83). Concerning effects of diet, see also the section on liver tumors.

Hormones.—These as physiological stimulants of certain organs facilitate carcinogenesis. There is also an intimate structural relationship between steroid hormones and some carcinogens (9). In addition to tumors of mammary glands, steroid hormones influence the occurrence of neoplasms of the cervix uteri, testis, hypophysis, prostate, adrenal, pituitary, uterine and extra-

uterine fibromuscular stroma, and lymphoid tissue. There are several excellent reviews on the subject (17, 84, 85).

Estrogens are concerned with controlled growth, imperfectly controlled growth, and uncontrolled growth (86). The controlled growth is confined to structures connected with sexual reproduction. The ability to respond to this stimulus is innate in each cell and is retained after transplantation. Excessive growth of breast in males (gynecomastia) in cirrhosis of the liver can be explained by diminished inactivation of the estrogen due to liver insufficiency. The imperfectly controlled growth provoked by estrogens includes uterine and extra-uterine fibromyomata of the uterus, ovarian cysts, chromophobe adenoma of the pituitary, and testicular adenoma. The uncontrolled growth includes leukemia, carcinoma of the breast, uterus, and bones, and sarcoma at the site of injection (86). Estrogens are powerful growth stimuli even to rudiments of the mammary gland in males, but they do not act in hypophysectomized animals (17). Breast tumors seldom occur in females castrated before puberty even if the animals are carriers of the milk influence. In mice, liability to mammary gland tumors increases with each pregnancy. Testosterone administered to virgin females lowers the incidence of breast tumors but is ineffective in breeding females (87). Long-continued treatment of mice with large doses of estrogens is followed by lesions of the cervix uteri grading from precancerous changes to squamous cell carcinoma (61). Neither the genetic nor the milk factor has much effect on this tumor (21).

There is a parallelism between the incidence of uterine tumors of rabbits and toxemia of pregnancy (88). Damaged liver fails to inactivate estrin which may rise in the blood to a carcinogenic level (88). Liver damage is, however, transient in toxemia; sustained liver damage, as with cirrhosis, is not known to be accompanied by more than slight gynecomastia in males.

Gonadectomy at an early age unmasks the powerful estrogenic potentialities of the adrenal. Adrenal tumors occur in old male guinea pigs and in mice that have been castrated when one to three days of age (17, 89, 90). These are associated with a state of hyperestrinization (91); evidently the hyperplastic adrenals were the source of the estrogen but the autonomous character of the adrenal growth remains to be proved. Excretion of excessive amounts of estrogens occurs even with masculinizing tumors of

the adrenals of man (91).

In male mice the administration of the estrogens stilbestrol (92) or triphenylethylene (93) leads to tumor-like growths of the interstitial cells of the testis. This is preceded by suppression of spermatogenesis and hypertrophy of Leydig cells. The latter become phagocytized by intertubular brown cells. New Leydig cells arise which grow rapidly and form disseminated nodules leading to enlargement of the testis. In some of these nodules cells become hyperchromatic and proliferate by mitotic division (92, 94). Metastases are occasionally noted, but attempts at transplantation were unsuccessful (93). This puzzle of lack of autonomy in the presence of invasiveness has been solved by the discovery that these growths require continuous estrogenic stimuli. When adequate quantities of estrogens are given to recipients, such grafts may take (94, 95). (See the section on autonomy.)

Long-continued hyperestrinization is productive of chromophobe adenoma of the hypophysis (25). Its incidence is greater among males than among females. Susceptibility to such tumors is partly inherited (25). In rats these adenomata may kill the host by compression of the cerebral peduncle and other parts of the brain (96). Attempts at transplantation into the usual sites have failed (96), but succeeded in the anterior chamber of the eye of rats (97). In hamsters, hyperestrinization produces enlargement of the pars intermedia (98) with invasion of the posterior lobe and neurohypophysis and the third ventricle. These changes are interpreted as those of heightened physiological activity and not a neoplasm (98).

Estrogens can produce fibroid growths not only in the uterus but also beneath serosal surfaces of the peritoneal cavity. Induction of such tumors succeeds readily only in female guinea pigs, and not at all in rats (99). The bulk of these growths is composed of fibrous connective tissue; muscle cells are occasionally admixed, while the serosal cells participate actively in their formation (100). Tumor induction is inhibited by testosterone propionate, desoxycorticosterone, estradiol benzoate (99, 101), and progesterone (102). Antifibromatogenic action parallels antiestrogenic effects in the guinea pig (103). Complete extirpation of the hypophysis or of ovary and uterus has no effect on this type of carcinogenesis (100).

Estrogens can be as powerful leukemogens as any other agent

known (60, 104). In animals treated with estrogens there is at first regression of thymus and probably of other lymphoid tissue, followed by hyperplasia; the leukemic cells arise in these damaged tissues (60). Leukemia is more common in female than in male mice (24). Castration of females lowers its incidence; castration of males raises it (105). There is a rise in the incidence of lymphomatosis in male fowls following castration (106, 107).

Females receiving *o*-aminoazotoluene are more susceptible to this chemical than males (108). Spontaneous hepatoma is most common in breeding males, least frequent in breeding females (109). The incidence of induced subcutaneous tumors is about 50 per cent higher in males (110).

Since estrogens are carcinogenic it can be supposed that a mechanism exists for their conversion into a noncarcinogenic substance and that disturbance of this mechanism may lead to neoplasms. Women with cancers of the breast are actually unable to convert estrone into estriol, the specific urinary metahormone in women (111). The fibromatogenic effect of estriol is less than that of estradiol and estrone (101).

Tumors are more frequent in old animals but grow better in young ones. Tumor induction by ultraviolet light and probably also by other agents takes a longer time in older than in younger animals (112). The slower regenerative capacity of tissues in older animals may in part explain this difference. The greater frequency of tumors in old age can be explained by the long latent periods required for induction of neoplasia.

The universality of estrogenic carcinogenesis is indicated by this survey. It is possible that as cocarcinogens, physiological quantities of steroid hormones share responsibility for the origin of many other spontaneous tumors.

Virus tumors.—The term virus is used by some to include hypothetical endogenous agents, perpetuating their kind autocatalytically; by others it is limited to minute exogenous agents, depending for their multiplication on living cells of higher organisms. Three types are known: (a) the chicken tumor agents, (b) the rabbit tumor agents, and (c) the milk factor in mice. These agents are of approximately the same size, and this is close to that of a macromolecular substance present in normal tissues. All three are species specific. The virus of chicken tumors multiplies perhaps exclusively in malignant cells, from which it can be ob-

tained in abundance. With few exceptions each chicken tumor agent produces precisely the same type of malignant neoplasm as that from which it was isolated. The milk factor can multiply in normal animals without producing a neoplasm, and it can be handed down to successive generations. It may reside in tumor cells, but there is no evidence that it is the immediate cause of the new growth or that it is responsible for its maintenance. The best studied tumor virus in rabbits produces papillomata similar to those that can be induced by chemicals; in these, carcinoma may arise, but from the latter the causative virus can not be recovered. Reports on the presence of similar virus in common tumors of rodents have thus far not been confirmed. Taylor (113) has grown mouse tumors in the yolk sac of the chick embryo and found that yolk sac centrifugate passed through Berkefeld N filter was capable of producing tumors. No single theory of cancer has been as ably supported by newer observations and theoretical considerations as the virus theory (10, 11, 12).

Chicken tumor virus.—Investigations on the chemical composition of these agents disclose a similarity to other viruses and to macromolecular substances present in normal tissues (114, 115), but the virus analyzed has not been freed from normal heavy materials. The latter are carriers of numerous enzyme systems. The virus protein can be distinguished from the normal heavy material by immunological means (115). The evidence that mitochondria yield heavy material is strong, but it is doubtful that all heavy material or viruses are derived from or related to mitochondria. The properties of the macromolecular material, are dealt with by Taylor *et al.* (116) and Kahler *et al.* (117) and in the reviews by Claude (114) and Kabat (115).

The problem whether these agents are variable as microorganisms or fixed is of interest. A permanent modification of the fowl tumor agent can be brought about by injecting it into ducklings less than twenty-four hours old (118). Some of the ducklings develop a hemorrhagic disease within a few days after injection (118) with no evidence of a neoplastic alteration. The modified virus fails to affect adult chickens but produces in ducklings a periosteal sarcoma. The evidence that the modified virus produces lymphosarcoma and a nonneoplastic bone proliferation (osteopetrosis) is not convincing, but it indicates the instability of fowl tumor agents and their capacity to undergo modifications. The charac-

teristics of the fowl tumor virus are somewhat modified through passage in turkeys and guinea fowls, but its species affinities are not modified (119). In the embryo the fowl sarcoma virus can be passed through numerous successive passages without eliciting tumors (120); hemorrhagic lesions may, however, occur. Another non-neoplastic change, bone proliferation with obliteration of the marrow and great thickening of the skeleton (osteopetrosis), can be induced by the agent of lymphomatosis (118).

Earlier observations on multiplication of the neoplastic chicken virus *in vitro* in the presence of normal cells have been confirmed (121). These studies are still fragmentary and require further elucidation. The same situation exists with respect to cancerization by virus *in vitro*. Normal cells, added to a culture of fowl sarcoma cells inactivated by doses of x-rays which do not destroy virus, are stated to acquire the properties of sarcoma cells (122). The former view that there is a wide gap between dosages of x-rays necessary to inactivate sarcoma cells and viruses has, however, been challenged (123). The recent observation that even normal cells may acquire malignant properties *in vitro* (49) necessitates reinvestigation of carcinogenesis *in vitro* by virus.

Rabbit papilloma virus.—The physical and chemical properties of this virus have been extensively studied (124 to 127). With respect to sedimentation rate, electrophoretic behavior, diffusion, and viscosity, it has the properties of a nucleoprotein similar to plant viruses. The mean diameter of the virus particles is 44 μ . The virus particles, originally thought to be spherical in shape (125), appear to resemble more nearly ellipsoids of revolution (126).

The papilloma virus has the essential attributes of common viruses. It produces complement fixing and neutralizing antibodies of the usual type in the tumor bearing hosts (128, 129). The antibodies are present mainly in animals with rapidly growing tumors. If antibody formation is related to immunization, one might expect the reverse, namely high antibody titre, in animals with regressing tumors (130). According to the theory of Rous, these viruses are ubiquitous normal inhabitants of the body, ready to act after some tissue derangement has prepared the soil for them. Virus and tumor cells may live in an enduring partnership with only immunological evidence suggesting the presence of the virus (131). Some caution is needed in accepting immunological evidence alone as indicating the presence of virus. Heterogenetic and

iso-antibodies will have to be considered. Discussion of natural antibodies that react *in vitro* with sedimentable constituents of normal tissue may be found in the work of Kidd & Friedewald (132).

Distinct from the papilloma virus are those producing fibroma and myxoma in rabbits, but it is still uncertain whether one of these can be transformed into the other (133).

Milk factor.—In following up experiments on the incidence of carcinoma of the breast in reciprocal crosses between inbred stocks of mice a maternal influence was disclosed which passes to the offspring with the milk (134). Although it is present in many other organs of the animal, including the blood, its natural mode of transmission is by ingestion of milk. It is passed to successive generations. The intensity of the milk factor varies in different strains of mice, as does susceptibility of different strains to the milk factor (17, 20). It remains intact in lyophilized milk, Seitz filtrate, and glycerolated tissue (135). It is readily sedimentable at 15,000 R.P.M. (136). Not all mice carrying it develop tumors, but all pass it unmodified to the next generation. These observations strongly suggest that it is a virus (137). It may arise *de novo* in animals of low mammary cancer strains (138). These observations should be further elucidated; do they mean sudden change in the enzymatic components of host cells resulting in the appearance of an autocatalytic agent, or contamination by an ubiquitous virus?

Minute quantities of milk ingested within a few hours after birth are sufficient for the transfer of the milk factor (139). Resistance to the milk factor increases with age (139). It can be transmitted by injection of blood or tissues from carrier mice, less effectively to older mice than to younger mice (140). It is present in spontaneous breast tumors in high concentration (141). Its presence raises susceptibility of the mammary gland to the induction of tumors by estrogens (16). The architecture of the mammary gland itself is altered by the milk influence (92).

There are hints that similar influences may exist in relation to other tumors, but with most neoplasms the results have been negative (142, 143). A maternal factor for leukemia is demonstrable by reciprocal crossings and by foster nursing, but this influence is slight and is not transmitted to successive generations (23). It is more marked in male than in female mice. In rare instances mice refractory to transmissible leukemia can be rendered susceptible by

foster nursing (144). It is possible that the milk factor can break down genetic barriers. Transfer of susceptibility of fibrosarcoma by transplanting impregnated ova from resistant parents to uteri of susceptible hosts was described by Cloudman (145). Further research on the existence of similar factors and on the character of breast cancer influence, its chemical components, site of origin, conditions of reproduction, immunological aspects, etc., are highly desirable.

Uterine influence.—Fertilized ova were transferred from mice of high cancer stocks into uteri of mice from low cancer stocks and vice versa (28). The mice so raised are subjected to all possible intra-uterine influences in addition to the milk factor. The change in the incidence of mammary tumors was greater in these mice than in fostered mice, a fact indicating additional intra-uterine influences; but simultaneous comparable data are not yet available.

Virus in chemically induced tumors.—The absence of a cell-free transmitting agent in chemically induced tumors has been indicated by the failure to isolate it by sensitive methods (37). On the other hand, immunological evidence has been presented (146) for the existence of an antigen in chemically induced tumors that is absent in normal chicken tissues but is related to a known chicken tumor virus. The problem is as puzzling as fundamental. The presence of an agent in tumors induced by chemicals recalls the phenomena of organizers (37), but it can also be supposed that the chemical merely prepares the soil for a virus. Description of virus in rabbit carcinoma and the virus theory of tumors is given by Rous (11, 12).

Tumors induced in sunflower plants by *Phytomonas tumefaciens* are also productive of secondary growths (147). When some of these are cultivated *in vitro* the causative bacteria are no longer demonstrable, but when these bacteria-free growths are implanted into sunflower or other closely related plants, they readily produce tumors (147).

Ultraviolet light.—Under standardized conditions it is possible to obtain an incidence of tumors, approximately 100 per cent, in the ears of mice by exposure to ultraviolet light (148). Tumor induction is dependent upon the total dosage rather than upon the intensity of the irradiation (138). The carcinogenic wave length of the spectrum lies between 2,800 and 3,400 Å. Other wave lengths,

while themselves not carcinogenic, may promote carcinogenesis (149). Once initiated, carcinogenesis proceeds without further exposure to light and sometimes several months elapse between last irradiation and appearance of tumors (150). The carcinogenic action of ultraviolet light is modified by accessory factors. Small amounts of energy applied over a long period of time are more efficient for tumor production than large doses given during shorter periods (151). The dosage rate and interval are important factors in carcinogenesis (151). It has been suggested that ultraviolet light converts cholesterol or another natural substance into a carcinogen (152). However, irradiated cholesterol is not carcinogenic and benzene extracts of the irradiated skin fail to yield a carcinogen. In support of the theory that ultraviolet light releases an endogenous virus, the experiments of Lambeau are cited (152), who demonstrated activation of latent herpes zoster virus by ultraviolet light; but virus has not been demonstrated in tumors induced by ultraviolet light, and the action of virus-induced Shope papilloma is not enhanced by irradiation. Ultraviolet light energy absorbed by nucleoproteins or chromosomal material may induce a mutation (152). The effects of ultraviolet light have been reviewed by Blum (153).

X-rays.—The carcinogenic effect of x-rays is conditioned by the state of the tissue. A single moderate dose of x-ray is capable of producing a malignant tumor if the irradiated tissue is inflamed at the time of its application, but not otherwise (154). The reverse is also true: doses of x-rays, themselves not carcinogenic, may enhance the sensitivity of the tissue for chemical carcinogens (155).

The pattern of multicellular growth can be profoundly altered by sudden derangement of nuclear substance by x-rays. The abnormalities in *Rana pipiens* following exposure of its sperm to x-rays have already been cited (35). Irradiation of eggs of strains of *Drosophila* with an hereditary tendency to tumors may raise tumor incidence from 15 per cent to 48 per cent at 1,500 r. No tumors are produced by similar irradiation of a nontumorous strain of *Drosophila* (156). The question is often raised whether an actual genetic factor for tumors exists or whether the inheritance concerns merely a propensity to development of tumors under given conditions.

Temperature.—This is one of the many known factors that in-

fluence the rate of development of tumors (149). Production of neoplasms in mice by ultraviolet light is more efficient at 35° to 38°C. than at room temperature, but there is little difference in the rate of tumor production at 3° to 5°C. and at room temperature; this may be due to an effective compensation by the mouse for the temperature. Similarly, high environmental temperatures increase the rate of development of tumors in the course of treatment with methylcholanthrene (149) and the growth of transplantable tumors as well (157).

Endogenous carcinogenesis.—The isolation of carcinogenic chemicals by Kennaway, Cook, and others led to the assumption that spontaneous and induced tumors result from the liberation of carcinogenic chemicals in the body. Since Kennaway demonstrated tumor production by pyrogenous products of cholesterol, numerous attempts have been made to convert substances present in the body into carcinogens. Schabad *et al.* have demonstrated repeatedly the presence in human liver and lungs of a material extractable by benzol and possessing carcinogenic potencies (158). This produces benign as well as malignant tumors in mice. More tumors are produced by extracts from the lungs of patients who have died of pulmonary or other neoplasms than by those from lungs of patients who have died of other diseases (158). The carcinogenic activity of liver extracts has been amply confirmed (159, 160). The active substance is contained in the nonsaponifiable lipid fraction of cancer-free livers of persons who died with carcinoma. Similar extracts from noncancer bearing persons had less carcinogenic activity (160). The reports concerning the presence of carcinogenic substances in cancers themselves are contradictory (160). Similar substances are present in the human gallbladder and in bile (161). The tumors produced by these agents occur at the site of the injection after a long period of latency; tumors at distant sites are not increased (162). It is assumed that the carcinogenic activity in extracts of these organs is not due to a pre-formed carcinogen but to a chemical conversion product (162). Production of neoplasms with materials from human sources has been reviewed (163). These studies are still in their infancy and, among others, data are needed on the relative quantity of carcinogenic substances in different organs of tumor bearing and normal individuals at varying ages, on the chemical structure of these substances, and on their relation to spontaneous neoplasms. Certain

food products when subjected to simple alterations may liberate carcinogens. Overheated cotton seed oil produces sarcoma in mice (164). Sesame oil that has been heated to 350°C. and benzene soluble fats from over-fried mixed meats (165) are capable of producing tumors. Previous studies have already shown that olive oil, linseed oil, and wheat germ oil behave in a similar manner (165).

THE COMPLEXITIES OF CARCINOGENESIS

The action of carcinogens is neither direct nor immediate. They either accelerate tumor development (166) or induce the development of neoplasms otherwise not seen in given strains. They may persist at the site of introduction and may be detected in the blood of numerous organs over long periods of time (167); or they may be demonstrable for only short periods of time in an unchanged form, being either converted into another substance which is responsible for the neoplasm or inducing a change which leads to secondary changes culminating in the development of tumors.

Pluripotentiality of carcinogens.—The first carcinogens isolated were known to affect only the skin at sites of application, but later the competence of their field turned out to be broad and variable. Multiple tumors at distant parts of the body (e.g., skin, stomach, lung, ureter) have been obtained in mice treated with polycyclic compounds of certain classes (168). 3,4,5,6-Dibenzocarbazole produces liver tumors, sarcoma at the site of injection, and epithelioma when painted on the skin (169). Leukemia is only one of several neoplasms which can be produced with methylcholanthrene (59, 170). 9,10-Dimethyl-1,2-benzanthracene accelerates the development of leukemia and mammary carcinoma in mice (166). Incorporation of 2-acetaminofluorene in the diet leads to an irregular epithelial hyperplasia in several organs, especially bladder, renal pelvis, liver, pancreas, and lung, and in numerous animals this goes on to an invasive growth (171). *o*-Aminoazotoluene, notorious for its ability to produce liver tumors, produces in addition sarcoma, hemangioma, and adenoma of the lung, all remote from the sites of administration (172, 173). Even ultraviolet light can induce tumors in a variety of tissues to which it penetrates, giving rise to sarcomas, muscle cell tumors, epitheliomas of the epidermis and its appendages, endotheliomas, and bone tumors (174). The most common distant tumor is that of the lung. Substances in-

jected reach this organ as readily as those inhaled. The neoplastic response of the lung is dependent upon the total amount of carcinogen reaching it. When the size of the particles injected is 10 to 20 μ , ten times as many pulmonary tumors are produced as when the particle size is 1 to 2 μ (175).

Co- and anticarcinogenesis.—Carcinogenesis is not an all-or-none phenomenon. The neoplastic potentiality of many agents is disclosed only under certain conditions. Trauma itself, for example, may not be conducive of tumor growth but facilitates localization of carcinogens (176, 177, 178), and the same may be true of physical agents such as ultraviolet light and x-rays, which produce a protracted trauma. Subcarcinogenic or threshold doses of physical or chemical agents spaced at proper intervals may hit a previously "sensitized" site and produce neoplasms. A single moderate dose of x-rays is capable of producing a malignant tumor if administered to inflamed tissues, but not otherwise (154). Pre-irradiation greatly enhances the leukemogenic action of methylcholanthrene (155). Subcutaneous tumors can be produced by the simultaneous injection of kieselguhr and *o*-aminoazotoluene (179). Croton oil and croton resin augment carcinogenesis when applied to the skin in conjunction with a dilute solution of benzpyrene. Two other skin irritants, turpentine and zylene, do not possess cocarcinogenicity (180). This is not a summation effect, since croton oil is not carcinogenic; nor is it mere nonspecific irritation. When applied to papillomas already established, croton resin appears to facilitate their conversion to malignant tumors (180). Scalding water may be cocarcinogenic under certain circumstances (152). Localization of tumors in scars and healing wounds, known after its discoverer as the "Deelman phenomenon," has again been demonstrated (178). Trauma alone does not produce tumor. The intervention of some specific agent is needed, and this may be exogenous or endogenous, localizing in the wound (181). In experiments of Rous *et al.* (177), there was a numerical increase of warts at the edges of the wound. Monochloracetone, an inhibitor of cell glycolysis, is capable in a wide range of concentration of stimulating tumor induction in mice that have received a preliminary but subeffective treatment with a chemical carcinogen (182). The solvent may be pro- or anticarcinogenic; e.g., sesame oil or arachis oil favor carcinogenesis, while mouse fat freed from phospholipins, ox brain, and

various lipins inhibit it (183). Diets high in fat accelerate carcinogenesis (79). Lard residue as a vehicle retards carcinogenesis by benzyrene, whereas lard filtrate promotes it. An excellent vehicle is tricaprylin (110). One cocarcinogen may not replace another during the precancerous period, but one carcinogenic hydrocarbon may do so (152). The aid of hereditary and hormonal factors has been discussed. Heredity, estrogens, and milk factor may all be essential to cause breast tumor, and it is merely speculative which is the immediate cause of it. Destruction of cells by x-rays is followed by a regenerative hyperplasia which is a fertile soil for carcinogenesis (155).

Carcinogenic influences in relation to virus tumor have been thoroughly analyzed (11, 177). Stimulated epithelial cells are more readily infected with virus and changed to neoplastic cells than normal cells. Susceptibility of the skin to the papilloma virus can be promoted by numerous substances, including chemical carcinogens. This is probably due to an increased number of young susceptible cells in this stimulated area (184). Dissimilar carcinogens may promote the action of each other. There is an intensified response to fibroma virus when tar is injected intramuscularly (152). Similarly, the Shope papilloma virus and tar are synergistic. Benign warts induced by tar become large and invasive after injection of the virus (176, 177).

The following are examples of anticarcinogens: benzene sulfochloride (185), potassium salt of the phytohormone (heteroauxin), potassium β -indolacetate (186). Several aliphatic and one aromatic acid chloride inhibit tumor induction by chemical carcinogens (185). A series of halogen compounds graded with respect to their power of checking cell glycolysis can retard the development of induced skin tumors (187). The sulphur metabolism appears to be intimately concerned in chemical carcinogenesis (187).

Several distinct steps are assumed to occur in the carcinogenic process and to these the terms pre-, epi- and metacarcinogenesis have been applied (188). Two carcinogens of the same or of different types may be synergistic or antagonistic, dependent upon their mode of action, the dose, and the time of administration. Carcinogens may also be indifferent to each other, e.g., ultraviolet light does not supplement the action of carcinogenic hydrocarbons when both are applied to the skin (152).

Liver tumor.—These can now be readily induced by pure chemicals under well controlled conditions, intermediate stages observed, and large quantities of tumor, pretumor, and homologous normal tissue collected for analysis. For studies on enzymatic and other chemical disturbances in relation to new growth, this material has proved extremely valuable. The production of liver tumors by *p*-dimethylaminoazobenzene and related compounds is a specific process. Indeed, this organ is resistant to direct application of carcinogenic hydrocarbons (189). Neoplasia is probably initiated in the course of the detoxification of these compounds and, if so, the conditions counteracting this type of carcinogenesis may also be effective in other processes of detoxification. The genesis of liver tumors is influenced by the physiological integrity of liver cells. In general, agencies which prevent liver damage and cirrhosis are also anticarcinogenic, but the parallel is not perfect (189). Cirrhosis of the liver induced by carbon tetrachloride is associated with formation of nodules of regeneration, but these seldom lead to truly metastasizing carcinoma (190, 191). Furfural, a component of sake, the Japanese rice wine, readily produces cirrhosis of the liver (192), and this is not preceded by demonstrable necrosis of liver cells. The mechanism of stimulation of connective tissue has not been precisely ascertained. Feeding seleniferous grains produces cirrhosis of the liver as early as three months after feeding, but adenoma or low grade carcinoma develops only after eighteen months (193). *p*-Dimethylaminoazobenzene, on the contrary, produces cirrhosis and carcinoma soon after administration, and carcinoma may occur even when visible liver damage and cirrhosis are minimized by administration of a protective diet (193). The new growth is usually preceded by adenoma-like hyperplasia in which the carcinoma arises after a long period of latency. Factors that retard carcinogenesis include the following materials active as dietary constituents: liver, yeast (189, 194), grains (195), casein and riboflavin (189), the combination of protein and B vitamins (195), and the combination of cystine and choline (196). The cocarcinogens include biotin (197) and cystine (198). Large amounts of pyridoxin in the diet lower the resistance to *p*-dimethylaminoazobenzene (189). Large amounts of riboflavin retard the induction of tumors (189, 199). Nicotinic acid retards somewhat tumor development, while thiamine does not alter the carcinogenicity of *p*-dimethylaminoazobenzene in rats re-

ceiving casein (189). The nutritional background of the animal is of some importance. Casein levels of 18 to 40 per cent offer partial protection against butter yellow. Dried liver is still more effective and its protective action is enhanced by riboflavin (195). A low cystine diet increases the latent period rather than prevents the formation of new growth (198). Methionine in place of *L*-cystine is likewise effective in raising the tumor incidence (200). The addition of choline and methionine to the diet prevents connective tissue overgrowth in the liver, but not the development of carcinoma (200).

An anticarcinogen may counteract the intracellular carcinogenic change or detoxify the carcinogen (e.g., the labile azo dyes) before it is able to act (195). Liver damage can be enhanced by dietary deficiencies. Fat made highly rancid with crude linoleic acid destroys butter yellow *in vitro* (201). Rice in the diet counteracts this destructive effect. Casein, and especially the combined oral administration of cystine plus choline, offer a definite but not regular protection against liver damage leading to carcinoma (196). On several diets cirrhosis is relatively mild, even though the incidence of tumors is high (189). The connective tissue overgrowth in liver is reversible (195).

Gastric tumors.—Neoplasia by *Spiroptera neoplastica* is still under debate. Ulcerative hyperplastic changes occur in the fore-stomach of rats with malnutrition or vitamin deficiency (202). When rats survive on a variety of unbalanced diets, proliferative changes develop, with the formation of papillomata. Casein and brewers' yeast are protective. Lack of vitamins A, B, B₂, C, or D are not responsible for these changes which are reversible on resumption of normal diet (202). Papillomata can be induced in the stomach of rats by feeding them with heated fats in addition to an adequate basal diet (203). However, this also produces A avitaminosis. Intestinal and other neoplasms develop in mice kept on diets containing carcinogenic hydrocarbons (204).

Brain tumors.—The possibility of inducing brain tumors has given an opportunity to study latent potentialities of cells of the nervous system and the histogenesis of an intricate group of new growths. Induced brain tumors have been identified as astrocytoma, oligodendroglioma, glioblastoma multiforme, medulloblastoma, spongioblastoma polare, ependymoblastoma, and unclassified glioma and sarcoma (205, 206, 207). Within certain limits

the site of the implanted pellet determines the type of the neoplasm. Many of these could be readily transplanted subcutaneously, even though they do not form extracranial metastases.

Bladder tumors.— β -Naphthylamine itself has carcinogenic properties apart from any impurities which may be present (208), but it is possible that one of its metabolites is the carcinogen (209). The epithelial changes induced range from simple hyperplasia to anaplastic carcinoma of the urinary bladder with infiltration of muscle and permeation of lymphatic vessels, but with no metastases.

Borderline, threshold, and latent neoplastic states.—Histologically it is not away possible to draw a sharp line between nodular hyperplasia and benign tumor, and between benign and malignant growth. Biochemical and biological studies have likewise failed to yield trustworthy criteria for their separation. A nodular overgrowth in the liver, "hepatoma," does not possess any significant metabolic or enzymatic deviation in the direction of a cancer (210). Autonomy is not an absolute property of neoplastic cells. Normal tissue is transplantable, but its growth is limited; hyperplastic epithelium, for example that of the gastric mucosa, already possesses a greater degree of "autonomy" than normal gastric mucosa. It grows in the lung after intrapulmonary transplantation, whereas normal tissue does not (211). Neurofibromas of the rat ear produced by ergot regress when ergot is withheld, reappear by refeeding, and, close to the end of the life span of rats, some regressed tumors begin to grow again (83). The dependence of Leydig cell tumors of the testis (26) on estrogenic hormones has been discussed. Possibly other benign and malignant tumors now regarded as possessing absolute autonomy are dependent on hitherto unknown factors essential for their maintenance and progressive proliferation.

Most benign tumors are not precursors of malignant growth. Nevertheless, upon continued animal passages they may undergo a carcinomatous transformation, e.g., breast adenofibroma (212) or pulmonary adenoma (52). Brain tumors (gliomata) are confined to the cranial cavity and are usually considered anatomically benign, though fatal to the host; but in the subcutaneous tissue they become aggressive (205).

Neoplasms are often preceded by a chronic tissue derangement, referred to as a precancerous state, in which some cells are altered,

though probably not yet neoplastic. Neoplastic potentialities are possessed not only by warts but also by the epidermis which takes their place following regression. On resumption of tarring or in response to noncarcinogenic stimuli, they readily give rise to malignant growth (177). The regenerated cell following injuries of different kinds is an altered cell, this being the MacNider phenomenon (56). Tumors may originate in such altered cells long after traumatization by burns, irradiation, or chemicals. At first there is tissue damage, followed by reparative hyperplasia never attaining a normal equilibrium. Here the cancer cell arises, either by step-by-step changes or by a sudden alteration resulting in abnormal differentiation or possibly a mutation. It is assumed (4, 213) that an interaction between carcinogenic, chemical, and protenoid constituents of the cell protoplasm has taken place, an "enzyme-virus" is formed (214), and this serves "as a model for its subsequent synthesis or reproduction by the cell itself" (213). If a sufficient amount of tumor protein is present, the cell is a part-tumor (213). Such alterations may change the immunological specificity of proteins, as the example of the Brown-Pearce rabbit carcinoma show (12). This leads again to the problem of viruses in relation to tumors from which they can not be isolated, brilliantly presented by others (11, 12), who believe that ultimate and direct power in the production of cancers is a virus.

With so many factors known to play some role in the causation of neoplastic growth, the direct cause of most tumors is still obscure. The breast tumor is a good example; each of the three main factors known, heredity, estrogens, and milk factor (17), has been regarded as the cause of it but all of them can be also considered as preparatory or contributory forces and the immediate cause of this neoplasm as unknown.

FACTORS PROMOTING OR INHIBITING NEW GROWTH

Carcinogenesis is concerned with the origin of the tumor cell and not with its continued growth. Carcinogens more often inhibit than stimulate growth. Experiments on the effect of carcinogens on normal growth have been reviewed elsewhere (39). Some stimulation has been obtained on tissue cultures of paramecia, bacteria, obelia, etc., and retardation on growth of rats, some spontaneous and induced tumors, tissue cultures, and sea urchin eggs. There is some correspondence between inhibitory and carcinogenic activity

of nearly-related compounds, and this relationship is probably of causal significance (215). Neoplastic cells are resistant to the inhibitory effect of carcinogens. Synthetic estrogens also inhibit growth. Their action is confined mainly to tissues and organs of the reproductive and endocrine systems (215). The growth controlling forces are extracellular, as indicated by the limitless growth of normal tissues in tissue cultures at almost the same rate as of malignant tissues (32). The embryo lacks some of the inhibitory factors possessed by the adult and allows the growth of some heterologous neoplastic cells and not of others.

The growth controlling forces are not of the same intensity in all parts of the body. In the anterior chamber of the eye some grafted cells, that are resisted in other parts of the body, proliferate. The results differ with different grafted and recipient tissues. Embryonal cells are more readily transplantable than adult cells. The growth requirements of transmitted tumors vary greatly with different strains of animals and different tumors. The main factors are those of heredity and the grade of tumor cell autonomy. The genetic factors are amply reviewed elsewhere (53). Genetic susceptibility to spontaneous tumors is different from that to grafted tumors. The genetic character of neoplastic cells varies and may or may not follow the pattern of normal cells (53). Hybrids may be highly susceptible to tumor grafts to which both parents are resistant (22).

Chemical substances.—Chemical substances that inhibit growth vary widely (216); these include: (a) heptaldehyde and compounds such as malonic acid and citral; (b) extracts of normal tissues, e.g., liver, muscle, and spleen extracts; (c) catalase poisons (in agreement with the idea that tumors are deficient in catalase); and (d) certain aromatic diamines. Of forty compounds tested (217) a marked inhibition on tumor growth was exerted by β -indolepropionic acid, β -indolebutyric acid, chloral hydrate, chlorotone, and sodium trichloroacetate. The technique used (mixing of chemical with tumor) is not a trustworthy indicator of growth inhibiting potentialities *in vivo*. Glycogen given intravenously significantly retards growth of tumors (218). Inositol, sodium phytate, and lipositol inhibit the growth of transmissible sarcoma in mice (219), as indicated by a test based on measuring the rate of tumor growth under standardized conditions (219). Benzol and potassium arseniate prolong the life of mice with transmitted leu-

kemia while numerous benzol substitution products and arsenicals proved ineffective. Different strains of leukemia respond differently to the same chemical (220). Purified synthetic amino acids are stated to cause disappearance of a transmissible sarcoma (221), but this observation requires confirmatory evidence. The mode of action of different chemicals is obscure, but some may influence tumor growth by a direct selective toxic action, e.g., N,N,N',N'-tetramethyl-*o*-phenylenediamine is about seven times more toxic to malignant lymphoid cells than to normal lymphoid cells (222).

Vitamins and other nutritional factors.—The growth of a sarcoma is arrested or retarded during a period of B avitaminosis with attending lowered body temperature, returning to normal on resumption of normal diet (223). Vitamin B₁ deprivation, quite apart from caloric restriction, retards the growth of a sarcoma (224). The growth rate of tumors is decreased in animals on riboflavin-deficient diet and increased on diet rich in this vitamin (225). Vitamin B₁ deficiency causes a significant decrease in the rate of tumor growth (226). Yeast prevents the growth of a transmissible tumor in about 20 per cent of the animals. Addition of pantothenic acid increases this figure to 47 and of riboflavin to 62 per cent. Thiamine has no effect (227). Yeast has an active principle that is not a known vitamin or a protein. It is water-soluble, thermostable, and can be precipitated with barium or ethanol (228). The effect of vitamin C is not consistent (229). Neoplastic cells seem to require larger amounts of vitamin C than nonneoplastic cells. Although some tumors are capable of maintaining their activity in biotin-depleted hosts (230), induced biotin deficiency may possibly explain spontaneous regression of some transmitted tumors (231). The biotin content of different tumors varies widely (230). By a combination of intravenous injection of yeast extracts with a diet of polished rice and carrot, numerous spontaneous breastcancers of mice may be caused to regress (232). Substances in various grains have a marked inhibitory effect on tumors (233, 234). The inhibition by certain compounds may be due to a specific deficiency in sulfur-containing amino acids produced by increased demand for organic sulfur for the detoxifying mechanism (3).

The retardation of growth in rats by diet deficient only in calories results in the postponement of neoplasms and other diseases occurring with age (73, 76, 77, 235, 236). Underfeeding alone

prolongs the duration of transmitted leukemia (220) and retards the growth of transmissible sarcoma (73).

Hormones and tissue extracts.—Neoplastic cells are not entirely free from controlling hormonal influences. Carcinoma of the prostate of man may become arrested at least temporarily by orchidectomy or by the administration of estrogenic hormones (237). Testicular tumors grow progressively only in mice that have received estrogens for several weeks, but may grow for a period of several months after the last injection and continue to grow if hypophysectomy is performed (26). The growth of transplants of benign fibroadenomata of the rat is under the influence of sex hormones (238). Large quantities of estrone may inhibit already established malignant growth to such an extent that the latter behaves as a benign neoplasm (239). Removal of the estrone pellet is occasionally followed by regression of the tumor induced by it (240). Progesterone inhibits the adenomatous growth of benign mammary tumor transplants; atrophy of the gland is followed by fibrous overgrowth. Progesterone also interferes with the success of the transplantation of these tumors. If administered in ratio of 18 mg. of progesterone to 1 mg. of estrogen, it inhibits the stimulating effect of the latter. On cessation of progesterone treatment, growth is resumed. Neither benign nor malignant connective tissue growth is inhibited by progesterone (238). Estrogen inhibits the growth of a transplantable carcinoma of the breast, but estrinized animals lose weight and this may account for some decrease in size of the tumors (241). The administration of estrogens produces secretory changes in the tumor cells, even in metastases, reminiscent of lactation, occasionally transforming the neoplastic glands into large cystic spaces (241). Some precancerous tissues can be transplanted in estrinized animals, but not in normal animals (242). Sex hormones also influence the growth of transmitted tumors whose origin is not related to them. Female mice are more resistant to a transmissible sarcoma than male mice, and castration increases the resistance of males and decreases that of females. This resistance factor passes to sucklings through the milk (243). Growth of some tumors is not under the control of hormones, which may have played a significant part in their genesis (244). Estrogenic hormones either inhibit growth of transplanted carcinoma of the breast or have no effect (241). Testosterone does not inhibit the growth of mammary gland tumors once these have reached

macroscopic size, but in young adult virgin females it lowers the incidence of spontaneous mammary gland tumors (87). A transplantable ovarian carcinoma grew only in males (26). The inhibition of growth by estrin may be due to an interference with pituitary function (3). In mice hypophysectomized during the latter half of pregnancy or postpartum, precancerous lesions of mammary gland do not undergo involution and mammary gland tumors continue to grow (26).

Splenic extracts are capable of bringing about regression of spontaneous mammary gland tumors of mice (245). The rarity of hematogenous metastases in muscles has long raised the question whether inhibitory substances exist in muscles; they have now been demonstrated in muscle extracts (246).

Growth-promoting substances liberated in tissue cultures of spontaneous mammary carcinoma promote the growth of fibroblasts (98), irrespective of the kind of tissue from which they were obtained or of its age; but they have no effect on the growth of normal mammary gland. This indicates that these malignant cells or their products do not induce normal cells to neoplastic growth and that the scirrhous character of some tumors may be due, not to replacement of dead cells, but to a direct stimulative effect on connective tissue by products of carcinoma cells.

Substances in the urine of patients with leukemia have a specific stimulating effect on hemopoiesis in guinea pigs (247). This lead is being followed up independently by Miller & Turner (248) and by Heinle, Wearn *et al.* (249), and their results are not in complete harmony. The former state that the stimulating lymphoid and myeloid substances differ chemically, though one can be converted into the other (248). The lymphoid stimulating substances are hydroxy-acids. The myeloid stimulating substances are non-carbinol acids; both are present in large quantities in the urine of patients with the corresponding type of leukemia and in small quantities in other urines. They assume that similar substances regulate normal hemopoiesis and that in the leukemias the ratios are disturbed. The urine of patients with monocytic leukemia or Hodgkin's disease is stated to contain both substances in about equal proportion (250). The foundation of this attractive theory (251, 250) does not appear to be solid. The character of the induced changes is not precisely described, and there is doubt that it is leukemia, as suggested (248, 250). On the other hand, the con-

clusion that extracts of urine from patients with chronic myeloid leukemia produce hyperplasia and myeloid metaplasia in guinea pigs with greater frequency than do extracts of controlled urines (249) is well supported.

The relation of age to tumor growth has long been known. In general young mice offer a better soil for the growth of transplanted tumors than do older mice; and young mice bearing spontaneous tumors are even better than normal young mice (252). This indicates the presence of growth stimulating substances in tumor bearing and in young animals or inhibitors in the old or the loss of some factors opposing growth in tumor bearing mice. Even tumors that appear in the very old, such as chromophobe adenoma of the pituitary, grow better in young animals (97).

Physical factors.—The effect of temperature on the rate of new growth in the frog is the same as on normal growth. Metastases occur more often and are more extensive at high (78°C.) than at low (4°C.) temperatures (253). Growth is checked during hibernation at 4°C. for eighty days, but no injury to the tumor results. At a higher temperature there is an earlier and more effective vascularization of the tumor (254). Regression of transmitted mammalian tumors occurs occasionally at very low temperatures (255). The limits of endurance for mice are eight to forty-eight hours in an environment of 5° to 7°C. Viability of the tumor cells is usually not affected at this temperature. The therapeutic experiments in man that have suggested this study have apparently been abandoned.

X-rays and radioactive substances are the best agents at present for the inhibition or control of malignant growth, and their effect can be readily demonstrated under controlled experimental conditions (220). This, however, may not be entirely growth inhibition, since these agents also destroy malignant cells, either by direct or indirect effect (123, 256, 257). Growth control by radioactive substances depends in part on the host's genetics. A given dose of x-rays (2,500 r) that controls growth in only 1 per cent of the parental stock controls it in 82 per cent of F₂ mice (258). Whether these interesting observations are applicable to spontaneous tumors depends on the genetic relation of the tumor cells to those of its host, and this is still a matter of controversy (53). Radioactive phosphorus is preferentially absorbed by malignant

tissues including leukemic cells and thereby selectively disturbs new growth (257).

CHARACTERISTICS OF THE NEOPLASTIC GROWTH

Malignant cells.—Malignant cells lack polarity, have a wide range of variation in nuclear and cytoplasmic structures, are not fully differentiated, are less dependent on oxygen supply than normal cells, are less under organismal control of cell division, are more easily transplantable, and are invasive (260). In epidermal hyperplasia produced by methylcholanthrene as compared with normal hyperplasia, there is a diversity in structures localized in foci of haphazard distribution (261). The focal variations in nuclear and cell size are of greater amplitude, and nuclear hyperchromatism and nucleolar size are sometimes increased. In methylcholanthrene hyperplasia there are local variations in mineral content, indicated by micro-incineration, not found in benign hyperplasia (261).

Chemical alterations in neoplastic cells are too numerous for a thorough review (1, 5, 6, 7). Numerous investigations have been directed toward the determination of changes in the enzymatic mechanism leading to metaplastic growth, and of similar changes in the tumor cells, and of systemic effects elicited by the tumor growth in various enzyme systems of the host (5). The latter roughly parallel in degree the growth of the tumors and are reversible with its removal. Earlier work suggesting that tumors have the same kind of enzymes as normal tissues was not based on analyses of homologous tumor and comparable normal tissue. Data on liver tumors are most valuable in this connection (5). Fetal liver resembles hepatoma more than it does either adult or regenerating liver, but fetal liver contains hemopoietic foci, and this may be responsible for some of the values (5). With few exceptions most enzyme substances normally found in the liver in large quantities are diminished in the hepatomas; these include: arginase, catalase, cytochrome oxidase, cytochrome-c, copper, and iron. Urea-synthesizing mechanism is absent, and the ammonia consumption is diminished. The urea content, on the contrary, is increased, as is proteolytic activity. No great difference is found in riboflavin and amylase values (5). Since hepatomas do not possess an oxidative reserve, they can supply energy only by an in-

crease in glycolysis (5). The free sulfhydryl content of hepatomas is about 24 per cent lower than that of normal rat liver (262). Degradation of cystine and related compounds is readily accomplished with extracts of normal liver, but not with those from hepatoma; thus, with the transformation of normal liver cells into tumor cells, more and more cystine may become available for the growth of hepatoma (263). The enzymatic change that affects a normal cell when it turns cancerous is not solely on the losing side. Experimental liver cancers in rats contain ten times as much alkaline glycerophosphatase as normal livers (264); similar findings were reported with phenylphosphatase (265). Differences in alkaline and acid phosphatase in liver tumors of mice and rats are discussed by Greenstein (265). Pepsin and phosphatase are decreased in gastric adenocarcinoma, phosphatase in intestinal adenocarcinoma, and depolymerase in lymphomas (5). The cytochrome-*c* content of tumors is lower than that of normal cells. This is cited to explain the high aerobic glycolysis common to most tumors (266). A series of papers has been published on the vitamin contents of tumors (267 to 270). The riboflavin level in liver tumors is less than in normal liver. The nicotinic acid tends to decrease in tumors. None of the growths examined was biotin-rich, and pantothenic acid was about normal. Induced gastric carcinoma has neither protease nor milk clotting activity. The thymonucleodepolymerase activity persists but in reduced amount (271).

Respiration, glycolysis, and respiratory quotient of malignant liver tumors are similar to those of other tumors, viz., high anaerobic and moderately high aerobic glycolysis combined with a respiratory quotient below unity (210). The viscosity of neoplastic liver cells is greater than that of normal liver cells, so that their nuclei and cytosomes fail to stratify upon high-speed centrifugation, as do those of normal liver cells (272).

Autonomy.—Growth autonomy is a relative term. Unrestrained growth occurs with both normal and malignant cells in tissue cultures. In the body both normal and malignant cells exist amid restraining and stimulating forces. Some of these are field forces, others, e.g., hormones, are more general influences present in varying quantities in the different sexes, at different ages, and in different individuals. Examples of hormonal control of existing growths have already been cited. Carcinoma of the prostate in man resembles in many cases adult prostatic epithelium that can be ac-

tivated by androgens and to some extent inactivated by castration or administration of estrogenic hormones. Castration in about 60 per cent of the patients with advanced and metastasizing carcinoma of the prostate is followed by disappearance of nearly all roentgenological and clinical evidence of tumor growth (237). Histological studies demonstrating the regressive changes that follow castration are not yet available. The response to orchidectomy is also manifested by drop of the acid serum phosphatase level of the blood, the source of which is the neoplastic tissue. Undifferentiated carcinoma is less under hormonal control (273, 274). Stilbestrol may act even when orchidectomy proves refractory (274), but its effects are only temporary, and its administration and discontinuance are reflected in alternate depressions and elevations of the phosphatase levels (274). In male animals the fibroadenomas often become transformed into pure fibromas, while in the female they retain their glandular components. This is due to androgenic hormones, which tend to transform the adenofibroma into pure fibroma (238, 275, 276). Progesterone inhibits the adenomatous elements of this growth, and fibrous over-growth follows. It also interferes with the success of the transplantation of this tumor, inhibiting the stimulating effect of estrogens (238). The findings with estrogen-induced fibroid growths are similar (102). Experimental testicular tumors grow progressively only in mice that receive estrogens for many weeks, but continue to grow for a limited period of time after the last injection and grow beyond that period if hypophysectomy is performed (26).

Chromophobe adenoma of the pituitary is common in old rats; it occurs with greater frequency in those treated with diethylstilbestrol for longer than a year. Though histologically benign, the tumor may be fatal to the host, causing compression of the cerebral peduncle and other parts of the brain (96). Nevertheless, attempts to transplant these growths have either failed (96) or succeeded only in the anterior chamber of the eye of homologous animals (277). A transplantable ovarian carcinoma grew only in male animals (26). Even certain precancerous lesions are transplantable into estrinized animals, but not into normal ones (242). Hyperplastic epithelium of gastric mucosa proliferates in the lung after intrapulmonary transplantation, whereas normal gastric mucosa does not (211).

The existence of field forces are suggested by the growth of

malignant cells in some sites but not in others after hematogenous dissemination. They are also evident upon transplantation of tumors that are restrained in one locality and assume the character of a malignant growth in another locality, e.g., pulmonary adenoma of mice (52) and brain tumors (205).

In studying tissue autonomy and in searching for field forces, homologous and heterologous transplantations of neoplastic tissues have been made in different sites of adults and embryos, and, vice versa, embryonal tissues have been implanted into tumors. For a more complete survey of these researches from the standpoint of embryology, see Needham (9) and Briggs (34, 278, 279). Hetero-transplantation of mammalian tumors has met with limited success. This depends on the growth requirements of the implanted tissue and on the antagonizing forces (local and general) of the recipient. Grafts of human cystadenoma of the ovary grow in the neighborhood of the kidney of mice after a lapse of three months (280).

Kidney carcinoma of the frog grows well in the dorsal mesenchyme of young tadpoles, but regresses rapidly as the hosts approach metamorphosis. The early environment exerts no morphogenetic or growth controlling effect on the carcinoma (278). Regression is not due to the same forces that bring about metamorphosis but is incidental to metamorphosis and is probably due to factors that bring about regression of grafts of incompatible tissues (278). The larval host is more favorable than the adult for the growth of adenocarcinoma from adults. Transplants in adults will grow in the anterior chamber of the eye, while those in the lymph sacs, cranial cavity, and abdomen become resorbed. In the tadpole minute implantations grow to sizable tumors in all of the above sites (279). In the chorioallantoic membrane of chick embryos, human leukemic leukocytes (281) or fowl leukosis cells (282) may grow for a short period without producing a leukemic change. Mouse and rat tumors grow readily in the yolk sac of the chick embryo (283, 284). On the chorioallantoic membrane some mammalian tumors proliferate rapidly, while others fail to grow (105). Morulae and blastulae of anuran amphibia transplanted into frogs give rise in many instance to round cell sarcoma-like structures (9). Implantation of pieces of mouse embryos into mouse fibrosarcoma may lead to teratoma-like formations (9).

Different rabbit tumors can readily be carried in serial passages

in the anterior chamber of the eye of the guinea pig and swine. They never metastasize, and attempts to transplant tumors to other sites from the eye of the guinea pig did not succeed (285). Malignant human tumors from the breast and colon, and melanotic and fibrosarcomas could be successfully transplanted in the anterior chamber of the eye of guinea pigs (286). Transplantation of human fibrosarcoma in the eye of guinea pigs has been carried out in serial transfers (287). Metastasis has not occurred. These heterografts, unlike tissue cultures, are supplied with stroma and blood vessels by the alien host; ability to survive and proliferate in an alien host is, however, not limited to malignant growth. Heterologous and homologous transplantation of embryonal tissues in the anterior chamber of the eye and testicle of rabbits and guinea pigs, including total embryos, has also been successful (288). Some of the resultant growths resembled teratoma and could be transferred serially; others underwent differentiation and resembled mature structures. Transplants were successful with most organs tried, but not with liver and organs of internal secretion. Thus, embryonal tissues have greater power to survive heterologous transplantation than normal adult tissues but not as much as malignant tissues. The skin and cartilage are particularly apt to grow in alien species.

The link between a developmental disturbance and neoplasia is formed by teratomas. Unlike common neoplasms, the teratomas are composed of more than one type of cell, and the constituent elements are foreign to their sites of occurrence. Two mechanisms might reasonably explain the occurrence of such an ontogenic fiasco, and both may hold for given teratomas: (a) abortive parthenogenesis and (b) inclusion of isolated blastomeres (31). The older work has been reviewed by Edmonds & Hawkins (31). The incidence of twinning is high in families with ovarian dermoids or childhood teratomas and twin pregnancies, higher in each instance than in a random control group. Teratomatous tumors are related to twinning and may involve common factors of heredity (31). When embryoma is transplanted serially, some embryonal cells multiply by mitotic division and exhibit their pluripotentiality by differentiation in various directions (289). Differentiation marks the end of the sideline. Among the progeny there will be also undifferentiated cells which carry on the growth. The metabolism values of this tumor are like those of true tumors (289). Embryonal nephromas of rabbit kidney have been transplanted in the anterior

chamber of the eye (290). This tumor has a close resemblance to rapidly growing embryonal renal tumors of man, yet it grows very slowly after homologous intraocular transplantation (290).

CLOSING COMMENTS

The primary change in new growth is within the neoplastic cell. The forces that produce it are as numerous as those responsible for cell variations and mutations. Some of these forces are genetic, others extrinsic or environmental. The carcinoma cell constitutes a new cell type within a given host with a varying degree of deviation from normal and limitation of freedom from forces controlling normal growth. It is uncertain whether this abnormal differentiation is accompanied by a chromosomal change, in other words, whether the neoplastic cell is a mutant. The phenomenon of neoplasia is universal. If viewed in the light of a growth disturbance, the diverse theories of neoplasia are complementary and its problems are those of biology.

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PHYSIOLOGICAL EFFECTS OF HEAT AND COLD

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This review deals chiefly with papers published in the British and American journals between August 1, 1942 and August 1, 1943. Papers which are primarily contributions in bacteriology, biochemistry, ecology, entomology, protozoology, pathology, and related fields or which were available only in abstract form in general were not reviewed. Certain relevant topics have been treated quite fully in recent reviews and therefore are omitted in the present discussion. Thus the reader is referred to the reviews of Gunn (1) on body temperature in poikilotherms, of Sizer (2) on the effects of temperature on enzyme kinetics, and of Weymouth, Kleiber, and Simonson in the present volume. Much material dealing with the heat production aspect of temperature regulation is presented by Kleiber, while the influence of heat stress on human subjects at work under varying environmental conditions is considered by Simonson and also in the very recent review of Bean & Eichna (3). Likewise the reader is referred to the nine recent reviews in Biological Symposia (4) for the literature on the effect of temperature on gene and chromosome mutation and on developmental processes generally. These nine papers were recently reviewed by Ephrussi (5). In this paper the sections on excised tissue and on hypothermia are relatively large, the former because it has not been reviewed before, the latter because of its current importance.

EXCISED TISSUE

The influence of temperature and other factors on the oxygen uptake of minced cerebral cortex from infant and adult rats was investigated by Himwich and his associates (6). It was found that either rise in temperature or suitable concentrations of potassium and paraphenylenediamine had less effect on the oxygen uptake of preparations of infant than of adult brain. It was suggested that these differences were attributable to a lower concentration of oxidative enzymes in the tissue of the newborn. The rapid increase in concentration of protein in the brain of the rat during early neonatal life is in harmony with this view. The influence of tempera-

ture on excised tissue has been studied by Fuhrman & Field and their associates. The oxygen uptake of bass (*Huro salmoides*) brain suspension and of rat cerebral cortex slices was measured at graded temperatures ranging from 5° to 40°C. (7). The curve of oxygen consumption as a function of temperature was similar in shape for bass and rat brain; the optimum temperature for the former being about 35°, for the latter 40°C. or slightly higher. Over the range 10° to 35° the oxygen consumption of both tissues was an exponential function of temperature. The van't Hoff coefficients (Q_{10}) were constant over this range, being 2.10 and 2.29 for rat and bass brain respectively. Thus, while the oxygen consumption of rat brain was greater than that of bass brain over the entire temperature range up to 35°C., increasing temperature augmented the oxygen uptake of bass brain relatively more than that of rat brain. The rate of ammonia production in excised bass brain increased with rise in temperature in the range 35° to 40°C. in which the rate of oxygen consumption is decreasing, possibly because of increased catabolism of some nitrogenous compound important in cell respiration.

The reversibility of the effects of extreme cold on the metabolism of the brain and kidney was investigated by Fuhrman & Field (8). Measurements of the rates of oxygen consumption and anaerobic glycolysis in cerebral cortex and kidney cortex slices from adult albino rats were made for successive periods of one hour each at temperatures of 37.7°, 0.2°, and 37.7°C. Under the conditions of these experiments these metabolic reactions returned to their initial rates on rewarming. However, when cerebral cortex slices were exposed to the 0.2°C. level for periods of 3, 5, 7, and 24 hours, the rates of oxygen consumption observed during a subsequent period of one hour showed progressive decrease. If respiration of the brain follows the same course *in vivo* and *in vitro* and if recovery of a normal level of oxygen consumption implies recovery of other functions of the brain, then it follows that death of the intact rat in severe acute hypothermia is not attributable to direct and irreversible effects of cold on the brain but to other factors. Unpublished work of J. M. Crismon (Stanford) has provided evidence that the crucial factor in acute hypothermia is failure of the great supply systems, the circulation and respiration. His observations indicate further that respiratory failure may well be due primarily to circulatory failure rather than to the direct effect of cold on the respiratory center. This is in consonance with the findings of

Fuhrman & Field (8) on the reversibility of inhibition of brain respiration by cold described above.

The influence of temperature on the augmentation of the oxygen consumption of isolated rat brain and kidney by 2,4-dinitrophenol was also investigated (9, 10). It was found that when the concentration of dinitrophenol in the respirometer vessels was $3.35 \times 10^{-5} M$ there was a 48 per cent rise in the oxygen consumption of cerebral cortex slices at $37.5^{\circ}C$. This augmentation in respiration became progressively greater in a relative sense (as per cent of control) with diminution in temperature, reaching a maximum (88 per cent) at 32° . With further fall in temperature the percentage rise in oxygen uptake due to dinitrophenol declined. The oxygen consumption of kidney cortex slices was actually slightly depressed by $3.35 \times 10^{-5} M$ dinitrophenol at $37.5^{\circ}C$., but was augmented at lower temperatures. In this case the maximum percentage effect was at about $22^{\circ}C$. Using graded concentrations of dinitrophenol it was found that the optimum concentration for the augmentation of oxygen consumption in cerebral cortex was approximately the same at $37.5^{\circ}C$. and $25^{\circ}C$. Both the percentage increase induced by the optimum concentration of the drug and the minimum inhibitory concentration were considerably greater at 25° than at $37.5^{\circ}C$. (9). These observations are in accord with the earlier work of Hall, Crismon & Chamberlin (11) on the intact cat.

The influence of cold on the inhibition of the oxygen uptake of rat cerebral cortex slices by two substituted oxazolidinediones, propazone (5,5-di-n-propyl-2,4-oxazolidinedione) and diphenyl-oxazolidinedione (5,5-diphenyl-2,4-oxazolidinedione) was also studied by Fuhrman & Field (12, 13). These substances are related chemically to the barbiturates and the hydantoinates. However, there are interesting differences in their pharmacological action. Propazone is a central nervous system depressant while diphenyl-oxazolidinedione in suitable dosage produces convulsions and death (in the mouse) without previous narcosis (14, 15). At $37.5^{\circ}C$. concentrations of propazone caused progressive reduction in the oxygen uptake of brain slices but the diminution with increasing concentration was rather gradual, until a level of oxygen consumption was reached which was not affected by a further fifty-fold increase in propazone concentration (inhibitor stable level). A different picture was obtained with diphenyl-oxazolidinedione.

With increasing concentration of this drug there was first a moderate augmentation, then a sharp depression of oxygen uptake. The inhibitor stable level was reached at a concentration of $6 \times 10^{-3} M$. A corresponding concentration of propazone caused only about 30 per cent inhibition. The bearing of these observations on the pharmacological action of the drugs was considered. The fraction of the oxygen consumption of cerebral cortex slices which was stable toward these inhibitors was also relatively stable toward cold. Thus while only about 10 per cent of the oxygen uptake was stable toward diphenyloxazolidinedione at $37.5^{\circ}C$., at 15° this fraction was 36 per cent. This inhibitor-stable and relatively cold-stable fraction of brain respiration was characterized by a low Q_{10} (about 1.3) and a low respiratory quotient.

The influence of supranormal temperatures on the oxygen consumption of rat cerebral cortex slices suspended in Ringer's solution was studied by Field, Fuhrman & Martin (unpublished). At $40^{\circ}C$. oxygen consumption was constant for an hour or more in about half the measurements; in the other half there was moderate decrease with time beginning as early as thirty minutes after thermoequilibration. At temperatures above 40° , ranging up to 47.5° , the diminution in oxygen uptake with time was progressively more rapid as temperature rose. The curves of oxygen uptake as a function of time became asymptotic to a level of about 10 per cent of the oxygen consumption of control brain slices maintained at $37.5^{\circ}C$. This thermostable fraction of the respiration was unaffected by high concentrations of propazone or azide. It was of the same order of magnitude as the fraction stable toward various chemical inhibitors at $37.5^{\circ}C$. It was suggested that the same group of processes constitute the thermostable fraction of brain respiration, the fraction stable toward chemical inhibitors, and also that relatively stable toward cold.

These observations do not support the often quoted statement of Dixon (16) that in excised brain "... a rise in temperature from 37° to 42° only produces a very slight increase in metabolic rate whilst on raising the temperature to 45° the metabolism increases enormously." Such a discontinuity in the metabolic rate-temperature curve is *a priori* unlikely because it has not been found in many previous investigations of the influence of temperature on metabolism or other processes in organisms or isolated organs (17). Thus no such discontinuity was apparent when the

0 to 20 minute oxygen uptake of rat brain brei (18) was plotted as a function of temperature or in measurements of the oxygen consumption of minced frog brain at different temperatures (19). In our opinion the data of Dixon were too few and too variable to serve as the basis for such a generalization.

The reversibility of the inhibition of the oxygen uptake of rat cerebral cortex slices by heat was also studied by Field, Fuhrman & Martin. Under the conditions of their experiments complete recovery of the initial rate of oxygen consumption occurred after exposure of cerebral cortex slices to 40°C. for as long as three hours. However, after thirty minutes at 40.8°, recovery was incomplete and longer exposures at this or higher temperatures resulted in progressively less recovery of the capacity for oxygen consumption when the tissue was returned to a temperature of 37.5°C.

Brachet & Bremer (19) undertook to determine whether the onset of heat narcosis in the frog, marked by a sharp decrease in the amplitude of the action potential of peripheral nerve, was also related to changes in the oxygen uptake of minced frog brain. They found that when this oxygen consumption was plotted as a function of temperature it showed a maximum at about 31°C. for *R. temporaria* and at about 38° for *R. esculenta*. Heat paralysis occurred in the former at about 33°, in the latter at about 39°. The similarity in these relations led Brachet & Bremer to conclude that there was a causal relation between the depression of brain metabolism by heat and the appearance of heat narcosis. Thermal depression of the respiration of minced frog brain was not found to be reversible.

The oxygen uptake of slices of liver, kidney, and the external and internal oblique muscles of the frog (winter variety of *R. pipiens*) was measured by Morales (20) at graded temperatures. He reported that the oxygen consumption-temperature curves were quite different for the organs tested and that all these curves differed from that obtained using the intact animal. An attempt was made to apply Crozier's method of thermal analysis to these data in conjunction with data of whole frog respiration and respiration through the skin (from the literature) to determine whether the oxygen consumption of a given tissue was limited by the availability of oxygen or by the characteristics of the metabolic machinery which uses the gas. In our opinion the fitting of the

Arrhenius plots (Fig. 5) is unconvincing and the elucidation of the problem posed above must await further investigation.

The effectiveness of low temperature in prolonging the survival time of isolated frog cardiac and skeletal muscle has been shown in an interesting preliminary paper by Spealman (21).

The influence of temperature on the retinal action potential in intact and deganglionated grasshoppers (*Melanoplus differentialis*) was studied by Jahn & Wulff (22). Earlier work indicated that removal of the optic ganglion was advisable for investigation of the uncomplicated retinal response. Temperature coefficients determined from measurements of the magnitude of retinal action potential were consistently higher for the light- than the dark-adapted photoreceptors. Both sets of temperature coefficients cannot be related to the same reaction of the visual mechanism. Reasons were given for assuming that above 15°C. the dark-adapted photoreceptor Q_{10} values pertained to the initial photochemical or light reaction, which is the master reaction in a catenary series, and that below 15°C. the Q_{10} values were those of the potential producing reaction, the master reaction in the low temperature range. Jahn & Wulff also suggested that the Q_{10} values for the light-adapted receptor represented the temperature coefficients of the dark reaction, the master reaction of the catenary series constituting the retinal mechanism in the light-adapted state.

INTACT ANIMALS

Oxygen consumption.—"The velocity of the catabolic reactions increases in all animals with rising temperatures up to a maximum at and above which the temperature has a deleterious effect upon the organism. . . . The more rigorously standard conditions are maintained the more regular is the influence of temperature observed" (23). This generalization has been challenged by O'Connor (24, 25, 26) and by O'Connor & O'Donovan (27), chiefly on the basis of measurements of the oxygen consumption of the frog and the earthworm at temperatures varying from about 1°C. to 31°C. On the basis of these findings they concluded that in the frog and earthworm oxygen consumption was not a continuous function of temperature over the range examined. O'Connor (25) stated that ". . . inquiry based on comparatively large numbers of observations shows that there are irregular increases and sharp falls

with rising temperature." However, O'Connor admitted that some of the alleged discontinuities were obscured by the wide scatter of the data and that: "It appears that the data could be represented in other and simpler ways and it has not been proved that this is not allowable" (25, p. 90). The reviewers do not concur with O'Connor's view that discontinuities in the oxygen consumption-temperature curve are established by his observations. It follows that the reviewers cannot accept O'Connor's ingenious interpretation of the effect of temperature on oxygen uptake. In our opinion both statements in the above quotation from Krogh still hold.

It has long been known that the influence of temperature on the metabolism of heterotherms varies from species to species. Recently it has been shown for several forms that the effect of temperature on metabolic rate depends in part on the temperature of the environment from which the animal is taken. The extent of this influence on the oxygen uptake of the sand crab, beach flea, and cunner has been studied by Irving and his associates at Swarthmore (for whom Noah's Ark would have been an appropriate location in the space-time continuum). At temperatures below 20°C. the oxygen consumption of the sand crab (*Emerita talpoida* Say) after allowance for differences in size, was greater in winter than in summer. The optimum temperature for oxygen uptake and the thermal death point (or range) were both lower in winter than in summer (28). This change in the properties of the biological oxidation system on long exposure to cold may be regarded as a primitive form of chemical defense, and the continued activity and growth of the sand crab during the winter indicate that it is an important adjustment of the animal to the season. No such seasonal influence on the effect of temperature on oxygen consumption was found in the beach flea (*Talorchestia megalopthalma*), an air-breathing neighbor of the sand crab. In line with these differences the beach flea, instead of remaining active during the winter, went into a state of apparent hibernation beneath the sand (29).

In the cunner (*Tautoglabrus adspersus* Walbaum) there was some adaptation of the oxidative metabolism to season, but this was less marked than in the sand crab. This is consistent with the observation that this fish leaves the cold shoreline waters in the winter (30). In these three studies oxygen consumption was ex-

pressed on a wet weight basis, although data on dry weight and percent digestible material were given for the sand crab (28) and the beach flea (29). The proportions of water and digestible material did not change with size (28, 29). However, no statement was made concerning possible changes in these factors with season. Interesting in this connection are the findings of Fuhrman & Field (unpublished) that there was significant increase in the percent dry weight in the bass brain in winter as compared with summer. Between 10° and 25°C. the oxygen consumption of the brain of winter fish exceeded that of summer fish on a wet weight basis, but there was no significant difference on a dry weight basis. While such considerations could not explain the notable seasonal differences observed in the sand crab (28), they might be involved in the story.

The influence of previous thermal experience on the oxygen consumption of fish has been investigated in the field by Sumner & Lanham (31). Using a single species (*Crenichthys baileyi*), animals previously living in a warm spring at 35° to 37°C. and in a cool spring at 21°C. were compared in respect of oxygen uptake when transferred from one environment to the other. Cool spring fishes died so rapidly in the warm spring that measurements of oxygen consumption were not practicable. When warm spring fishes were transferred to the cool spring they remained in good condition for several days and may do so indefinitely. After transfer there was a rapid fall in oxygen consumption and in a matter of hours the metabolic rate, for animals of the same size, was about the same as that of fish native to the cool spring. It was also noted that the temperature coefficient for oxygen consumption was higher for the smaller (younger) animals and that there was an inverse correlation between size and metabolic rate.

In a comparative study of the metabolism of a species of Pacific Coast termite (*Zootermopsis angusticollis*) and its cellulose splitting microfauna, Cook & Smith (32) reported that the influence of temperature was quite different in the two cases. In acute experiments the oxygen consumption of the termite increased with rising temperature over the range 4° to 32°, whereas the metabolic activity of the microfauna, as indicated by the hydrogen production, rose to a maximum in the range 16° to 24°. When the animals were exposed for several weeks to a range of temperatures, the metabolic effectiveness of the microfauna remained essentially

unchanged at 9°, 19°, and 29°, but was seriously impaired at 4°C. In the latter case the net respiration and the respiratory quotient of the termite both indicate a condition of starvation. This appeared to be referable to inanition due to the failure of the symbiotic protozoa.

Gordon & Pomerat (33) reported differences in the value of the Arrhenius temperature characteristic of the respiration of the newt when pentobarbital and chloretone were used as anesthetics. The range was 6.5° to 21°C. The bearing of these observations on the theory of anesthesia was discussed. The influence of temperature on oxygen uptake of the sloth (*Bradypus griseus* and *Choloepus hofmanni*) and the armadillo (*Dasybus novemcinctus*) was studied by Irving *et al.* (34, 35). These animals are deficient in respect of temperature regulation although they are not heterotherms. At air temperatures of 24° to 28°C. their rectal temperatures ranged from 32° to 36°C., and their oxygen uptake on a unit weight basis was low for animals of this size.

TEMPERATURE REGULATION

Development.—Most animals which are typical homeotherms in the adult state show poor capacity to regulate body temperature at or before birth and even during infancy. An important study on the regulation of body temperature in twenty-five premature infants has recently been reported by Day, Curtis & Kelly (36). All weighed less than 2,500 gm. at birth. At the time of observation their ages ranged from 4 to 53 days and their weights from 1,400 to 2,900 gm. Since all were thriving during the period of study the findings could not be extended without reserve to very feeble, sick, or smaller infants. Before the observations were begun the infants were kept in an air-conditioned nursery maintained at 24.5°. Sufficient clothing, together with local heating when necessary, had been used to maintain rectal temperature at about 37°C. During the investigation simultaneous measurements were made of six variables which determine heat regulation. These were heat production (indirect calorimetry), heat loss by radiation and conduction, heat loss by evaporation, rectal temperature, skin temperature, and activity. When heat production was plotted as a function of environmental temperature over the range 26° to 34.5°C. (omitting instances of active sweating) a good approximation of a straight line relationship was obtained. The negative

slope indicated the presence of some degree of chemical regulation, i.e., an increase in metabolic rate above the basal level when a resting and fasted animal is exposed to cold (37).

The several components of chemical regulation, thermal tone, action of calorogenic hormones, and shivering, were not differentiated satisfactorily because observations on activity were merely subjective estimates. When body size was excluded by calculation of the partial coefficient of correlation of heat production and air temperature at constant body weight the data still indicated decrease in heat production with rising environmental temperature in the range studied. In the cold the chief handicaps of the infant were relatively large surface area, poor insulation, and weak musculature. No defect in vasoconstriction was evident. In warm air the chief defect in temperature regulation shown by the premature infant was an inadequacy in sweating. No defect in vasodilation was evident.

The development of temperature regulation in birds has been studied by Odum (38) and by Randall (39). In several species the development of capacity for temperature regulation coincided closely with the appearance of coordinated muscular tremors. This cold defense mechanism involving increased muscular activity appeared to develop before and (at least at first) more rapidly than the physical defense against cold provided by feather growth (39). The newly hatched chicken (*Gallus domesticus*) showed little capacity for cold defense. By seven days of age vigorous shivering occurred on exposure to cold but adult capacity for cold defense was not present until the down feathers were well replaced by adult plumage. In seven-day old chicks shivering could be evoked either by cooling the skin with little or no change in body temperature or by falling body temperature without change in skin temperature. "It therefore appears that shivering may be produced reflexly by stimulation of the cold receptors in the skin or centrally by cooling effects of the blood bathing the thermogenic centers." In contrast, warming the skin (4°C.) without change in body temperature did not evoke panting, but panting did occur as soon as body temperature was raised (39).

Brody (40) investigated the development of temperature regulation in suckling rats. Shivering and other muscular reactions to cold became apparent at about nine days of age. Adult regulation was rather completely attained in twenty-two days (at weaning).

Normal temperature levels.—Hersh, Woodbury & Bierman (41) showed that a difference of more than 3°F. exists between the coolest and warmest regions of the human mouth. In order of increasing temperature these were the hard palate, soft palate, oral gingiva, distal portion of the tongue, midportion of tongue, proximal portion of tongue, buccal mucus membrane, alveolus, and sublingual area. Many measurements of rectal and skin temperature in premature infants are given in the paper of Day *et al.* (36). The rectal temperatures of 107 mongrel adult dogs, quiet and in good health, were measured by Friedman & Bennett (42). A group kept in an air-conditioned building had the same average rectal temperature, 102.0°F., as a group not so treated. The range in the whole series was 99.9°F. to 104.8°F. No significant differences were noted between the sexes or between short and long haired types.

Brennaman (43) reported that in ten children and three adults oral temperature showed little change or even dropped after exercise while rectal temperature rose. However, decrease in oral temperature after exercise has been known to physiologists for over one hundred years (44), and the rise in rectal temperature during and after exercise has been studied extensively (45, 46).

Nervous mechanism.—This topic is reviewed by McSwiney in the present volume.

Experimental modification of threshold.—In domestic fowls (*Gallus domesticus*) hypothermia was shown to lower the threshold temperature for panting, so that panting occurred as body temperature approached normal rather than when the normal level was exceeded. In contrast, hypothermia decreased the sensitivity of the shivering mechanism, so that body temperature fell more rapidly on exposure to cold (47).

Heat loss: panting.—Hiestand & Randall (48) studied the influence of proprioceptive vagal afferents on panting and accessory movements in rabbits and chickens. Unilateral vagotomy reduced the respiratory rate more in the chicken than the rabbit. After bilateral vagotomy respiration was further reduced in both forms but more notably in the chicken. The vagotomized rabbit could pant normally. The vagotomized chicken could not pant at all. Although the proprioceptive drive is clearly greater in the bird, distention of the lungs by emphysema (air forced into tracheal cannula during polypneic breathing) was more effective in reducing respiratory rate in the rabbit than the chicken. It was sug-

gested that the stimulus of emphysema differs from the usual lung stretch effect or that different types of receptors occurred in the lungs.

Heat loss: peripheral blood flow.—Barcroft & Edholm (49) studied the influence of water bath temperatures ranging from 13° to 45°C. on blood flow and deep temperature in the human forearm. Flow-time relations were considered with reference to three temperature ranges: (a) 13° to 35°C., in which the flow remained quite constant after the first fifteen minutes. (b) 37° to 42.5°C., in which the flow rose to a maximum in periods which shortened as external temperature rose. Progressive diminution followed this peak. Thus no steady state was attained. Factors possibly contributing to this effect were discussed. (c) At 45°C. the blood flow rose to a maximum in about thirty minutes, then remained at this high level or even increased slightly. In general, spontaneous variations in blood flow were more frequent the higher the water temperature.

At least five factors influence the deep muscle temperature: (a) waterbath or environmental temperature; (b) exposure period; (c) rate of blood flow; (d) body temperature; and (e) local metabolic rate. In water baths below 35° attainment of a steady deep muscle temperature required an hour or more; at 13°C., about two hours. Equilibrium was reached within an hour at bath temperatures above body temperature. The steady state of deep muscle temperature was 4° to 5° higher than a water bath of 13° and about 2.5° above baths at 20° to 32°. The rapid initial fall in baths below 20°C. was due to the greatly decreased blood flow. When water bath temperature equalled body temperature the deep muscle temperature was about the same. At higher bath temperatures the rise in muscle temperature decreased progressively with each increase in bath temperature. The steady state was usually the same, 39°C., at bath temperatures of 42.5° and 45°. In some instances deep muscle temperature diminished on raising the bath from 42.5° to 45°C., because of the greatly increased blood flow at the higher temperature. In the cold baths (13°) the sensation of cold lasted only about ten minutes. There was no discomfort but when the arm was taken out after two hours or more, muscular movements were difficult and slow. There was no generalized shivering. Immersion of the forearm in warm baths caused a small, sharp rise in body temperature as the large volume of blood flowing

through the arm was heated followed by a plateau and a fall. However, the body temperature differed by only about 1°C. from the arm in the coldest and hottest baths employed. Barcroft & Edholm pointed out that the increased blood flow through the arm at high temperatures almost certainly involved vessels in the muscles as well as the skin.

Paralysis of the sympathetic supply of the right arm by novocain (paravertebral route) caused the same increase in blood flow in the right hand as immersion in water at 43°C. (50). It thus appeared that inhibition of sympathetic activity could account for full vasodilation in the hand and that there was no need to assume that sympathetic nerves to the hand contain vasodilator fibers. Similar evidence was provided for the absence of vasodilator fibers in the sympathetic nerves to vessels in the forearm.

Peripheral vasodilation or vasoconstriction produced by warming or cooling the human body caused only minor changes in cardiac output (51). This was attributed to the buffering capacities of the vasomotor system.

Heat loss: anesthesia.—Notable rise in skin temperature due to dilatation of peripheral vessels was observed in normal subjects on inhalation of nitrous oxide, ethylene, cyclopropane, ether, and chloroform. The effect occurred in the first plane of anesthesia if maintained for several minutes. There was no fall in arterial pressure. Cutaneous vasodilatation also followed spinal and local block anesthesia. Spinal anesthesia to the level of T₁₀ was adequate to produce a maximum effect. Failure of this response proved of value as a guide in the differential diagnosis of occlusive and spastic peripheral vascular disease (52).

Heat loss: sweating.—Burch & Sodeman (53) have studied the variations in the rate of sweating on skin surfaces of different parts of the body under standard conditions in a subtropical climate at different seasons. In a comfortable air-conditioned room the most rapid rates of insensible perspiration were from the hands, feet, forehead, and cheeks. Insensible water loss was relatively slow from the skin of the trunk, arms, and legs. There were marked variations in the rate of insensible water loss for the same area from subject to subject and from time to time in the same subject. In a hot, humid room there were marked spatial variations in the rate of sensible perspiration, often notably involving those areas which showed little insensible water loss in the previous ex-

periment. There was no definite evidence of difference in the rate of insensible or sensible water loss as between winter and summer when measurements were made under constant laboratory conditions.

Heat production: role of viscera.—Federov & Shur (54) found that in normal fasting dogs the lowest temperature of the blood was found in the aorta and the highest in the hepatic vein. When the animals were cooled by placing ice on the skin there was a three- to six-fold rise in hepatic heat production when the blood flow was increased. In the hyperthermic animal the reverse change occurred. Homogeneous blood transfusion did not evoke noticeable changes in thermogenesis in the liver and the intestines despite a rise in systemic temperature. In contrast, fever caused by heterogeneous transfusion (goat blood) was accompanied by increase in heat production in the liver and intestines. After anaphylactic shock the same changes were observed as in the case of heterogeneous transfusions but the variations in temperature were much greater. The parallelism between the increase in visceral thermogenesis and rise in body temperature on administration of foreign blood suggested that the liver and intestines participated in the febrile process so evoked.

Heat production: shivering.—When body temperature was progressively reduced in the seven-day chick shivering began to decrease in intensity at about 26°C. and ceased entirely at about 20° (39). When the body temperature of the rabbit was lowered rapidly shivering sometimes persisted when the rectal temperature was as low as 10°C. (55). Evidently persistence of shivering depends on both the rate of fall (at least within limits) and the prevailing temperature level.

The metabolic cost of cold defense in the rat was nicely shown by the data of Black & Swift (56), presented in a graph of heat production as a function of environmental temperature. Feeding did not lower the temperature of minimum heat production below 30°C., the critical temperature for the fasting rat. At environmental temperatures below 25° the heat production of fed and fasted rats, corrected for weight, did not differ. Above 25° the heat production of fed rats was higher than that of fasting rats.

Endocrine factors.—Marked impairment of cold defense was observed in young rats after hypophysectomy (57). Improvement followed administration of crude pituitary extracts or purified

corticotrophin. The effect of these extracts was abolished by adrenalectomy but not by thyroidectomy. Adrenal cortical extracts increased the cold resistance of hypophysectomized rats and of hypophysectomized rats without thyroids or adrenals. "The protection against cold afforded hypophysectomized rats by pituitary extracts paralleled their corticotrophic activity and was attributed to the cortical function thereby induced." Zarrow (58) found that desoxycorticosterone acetate and progesterone, in suitable dosage, enabled adrenalectomized mice to survive exposures to low environmental temperature fatal to the untreated animal.

Dempsey & Astwood (59), in a paper which included a description of a new and precise method of thyroid hormone assay, based on the use of thiouracil, showed that a quantity of thyroid hormone equivalent to 5.2 $\mu\text{g.}$ of thyroxin daily was required to maintain a thyroid of normal weight in young male rats kept at room temperature averaging 25°C. In terms of thyroxine the daily requirement was 9.5 $\mu\text{g.}$ at an environmental temperature of 1°C. while at 35°C. it decreased to 1.7 $\mu\text{g.}$ The importance of potentiation of the calorogenic action of epinephrine by thyroid hormone in the cold defense reactions of the rat was pointed out by Ring (60). There is some uncertainty as to the time relations of thyroid participation in cold defense. The older findings indicate that this is rather slow. In consonance with these observations Leblond *et al* (61) found that exposure of adult rats to cold caused a rather slow increase in thyroid activity as evidenced by uptake of radioiodine. However, Ariel & Warren (62) reported that profound changes in the size of the follicular epithelium and in the follicular contents of the thyroid gland may occur even within half an hour in the various stages of experimental hypothermia in the rabbit. Possibly species differences obtain. Decreases in seminal vesicle and scrotal sac weights and in height of scrotal contraction occurred during the first, second, and fourth weeks after castration of the mature rat (63). These findings support the view that the development and control of the thermoregulatory function of the rat scrotum is dependent upon testicular hormone.

Metabolites.—An interesting instance of rapid adaptation of metabolic rate and body temperature to environmental conditions has been reported by Scholander *et al.* (64). The temperature in different parts of the body of the seal (*Phoca vitulina*) dropped

steadily during a dive. The decrease was greater in peripheral than in deep parts; occasionally there was no change in the region of the liver. This drop in body temperature during diving occurred in spite of marked diminution in peripheral blood flow. It indicated a decrease in heat production of 50 per cent or more. It was suggested that this decline in metabolism was attributable to accumulation of metabolites like lactic acid and to depletion of oxygen. The quickness of the drop was due to the rapidity of circulatory arrest in the tissues concerned.

Adaptation to climate.—Exogenous as well as endogenous factors have been shown important in the adaptation of the rat to long-continued thermal stress. Thus a heightened requirement for thiamine and choline, without change in the requirement for riboflavin, pyridoxin, inositol, *p*-aminobenzoic acid, and nicotinic acid, has been reported for young rats in tropical heat (65, 66). In a paper which the reviewers consider one of the greatest contributions of a biologist to human ethics, Allee (67) mentioned briefly the importance of social behavior in protection from thermal stress. Quantitative data illustrating the time-temperature relations of heat and cold tolerance and the influence of acclimatization in young greenfish (*Girella nigricans* Ayres) have been reported by Doudoroff (68). The ecological implications of these findings were discussed.

Variation in the reflex responses of the frog spinal cord and in the temperatures at which heat and cold paralysis develops has been described by Ozorio de Almeida (69, 70).

HYPOTHERMIA

With few exceptions only papers appearing since Herrington & Gagge's excellent review (71) will be considered here. Much of the research during last year on human adjustment to environmental stress will not appear until after the war. However, the urgency of the problems in this field has also led to the publication of much "open" information. Interest in hypothermia in nonhibernating mammals is not new. Boswell (72) in 1781, commenting on an early refrigerating device, spoke of: "... the art of congealing living animals in such a manner that they shall remain in exactly the same state they were in when the frigorific operation is performed. . . ." He suggested various practical applications of this technique, including induced temporary frigidity: "... when

a husband has his wife well frozen, he may go from home in full security. . . ." More practicable contributions on the use as well as the effects of cold were made by John Hunter (73, 74), Arnott (75), and Walther (76). During the year reviewed there were many contributions bearing on the therapeutic use of cold. Only a few can be considered here. However, various aspects of this subject have been reviewed by Allen (77), Smith (78), and in various editorial and current comment columns of the medical journals (79 to 88).

Anesthesia.—Instances in which cold was used for surgical anesthesia were reported by Hunter (74), Arnott (75) and Walther (76). No doubt this list is incomplete. However, present appreciation of the value of cold anesthesia stems from the pioneer work of F. M. Allen (89, 90). The importance of low temperatures in prolonging the viability of limbs with the circulation arrested by tourniquet was shown by Allen (90), Brooks & Duncan (91), and Blalock and associates (92 to 96). With this background, Crossman, Allen *et al.* (97) employed a tourniquet and refrigeration for the preparation of gangrenous limbs for amputation. They reported several advantages of this method including reduced incidence of shock. Details of method are given in a recent paper (98). Good results with cold anesthesia for limb amputations have also been reported by McElvenny (99), Mock & Mock (100), and others.

Wound healing.—Favorable influence of cold on wound healing has been reported by Allen and his associates (97), Sano & Smith (101), McElvenny (99) Mock & Mock (100), and others. The literature was recently reviewed by Smith (78).

Shock.—It was shown by Allen in his earlier work on the uses of cold that shock which follows release of a tourniquet applied for some time to the leg of a rat was reduced or abolished if the limb was kept cold during the period of ligation. These observations focussed attention upon the problem of temperature regulation in shock. Evidence supplied by the work of Allen (102) and of Blalock and his associates (93, 94) indicates that the use of external heat in the treatment of shock is unwise. There are at least two reasons for this. Rise in temperature in shock would increase any discrepancy between metabolism and blood supply at a time when the circulation is already impaired, and would interfere with the adjustment of the vascular bed to the diminished

blood volume. On the other hand present evidence does not indicate that body temperature should be lowered in shock (94, 102, 103, 104). Elman *et al.* (104) found that the most favorable environmental temperature for the survival of the rat after extensive body burns was 75°F.

Damage due to cold.—Long continued exposure of the extremities to cold or perhaps even cool water under generally adverse conditions gives rise to a syndrome known as "immersion foot" (83) or "peripheral vasoneuropathy after chilling" (105). Perhaps "immersion ear" would be more proper because the syndrome of persistent hyperemia and edema after immersion in cold water was demonstrated by John Hunter (74) in the rabbit's ear in 1778. The syndrome and suitable therapy have been described quite thoroughly in several papers (105, 106, 107). Essential features of treatment are slow rewarming to avoid an imbalance between tissue metabolism and blood supply, and avoidance of trauma to the skin.

General hypothermia.—Interest in this subject, stimulated by the pioneer work of Smith and Fay, reviewed by the former (78), continued during the year. The sequence of events during acute induced hypothermia in the normal rabbit was described by Ariel and his associates (55, 62, 108, 109). These studies were of particular interest because no anesthetic was used and the uncomplicated effects of hypothermia were thus observed. In large measure the picture was the same as that presented in the earlier papers of Britton (110) on the cat and Woodruff (111) on the dog. However, some of the rabbits were reported to have survived rectal temperatures as low as 10°C., far lower than reported for other nonhibernating mammals. Perhaps the absence of an anesthetic was important here. However it must be borne in mind that rectal temperature may not be representative of deep body temperature after rapid cooling in a water bath. The regions determining rectal temperature might be involved in thermovascular reflexes or the rectal temperature might participate in general peripheral cooling because of spatial relationships, or both factors may operate (112). During the first 2°C. fall in rectal temperature the rabbits were usually quiet, then shivering set in, with increased respiratory and heart rates. As the temperature dropped below 32°C. there was progressive and corresponding decline in both rates. Below a rectal temperature of 20° both respiration and heart beat became ir-

regular. This was very conspicuous at 10°C. An electrocardiogram taken at a rectal temperature of 20° showed a heart rate of 20 to 28 per minute (normal rate about 200), with complete heart block, prolonged QRS and ST intervals, and occasional ectopic ventricular complexes. In some instances cardiac function continued long after cessation of respiration, an effect reported before (110, 111). The temperature at which shivering disappeared was lower the more rapid the cooling. When this was pronounced some animals still shivered at a rectal temperature of 10°C. Deep reflexes disappeared below 20°C. Also below 20° several animals exhibited repeated, general clonic convulsions, lasting thirty to sixty seconds. This is reminiscent of the convulsions induced by sudden cooling of the frog spinal cord (69). Before and after such convulsions or in their absence the animal was atonic. Considerable individual variation was observed in the capacity of the animals for defense against cold. The rapid response of the thyroid to hypothermia was discussed on p. 83. In the twelve animals tested, rise in serum magnesium was demonstrated during hypothermia (109). Possible implications of this finding were discussed. Short periods of hypothermia (18°, 20°, and 30°C. for six, eight, and twenty-four hours respectively) had no definite lasting effect on the growth of Brown-Pearce epitheliomas in rabbits (108). However, there was more rapid development of metastases in the cooled animals. These results were not in harmony with those of Smith & Fay (78), but different species and different levels of hypothermia were involved.

The influence of hypothermia on resistance to infections was investigated in the rabbit and guinea pig by Hardy *et al.* (113, 114, 115). Phenobarbital anesthesia was used. When guinea pigs were infected subcutaneously with virulent human tubercle bacilli two twenty-four-hour periods of hypothermia a week for six weeks did not affect the amount and distribution of tuberculous involvement of the various organs as found at necropsy. However, tuberculin reactions were less marked in the treated animals at least during the period of intermittent hypothermia (114). More striking results were obtained in rabbits inoculated intradermally with cultures of (a) a highly virulent strain, or (b) a relatively avirulent strain of pneumococci and subsequently cooled to 31° to 33°C. for six to forty-eight hours. In the first group survival time was short in both untreated and chilled animals; the only significant difference was a less severe local inflammatory reaction in the

latter. However, when avirulent pneumococci were used in doses not lethal under ordinary conditions, hypothermia usually resulted in overwhelming bacteremia and death (115). Local chilling at the site of inoculation had no such effect. Furthermore it was shown that mortality was increased if the animal's temperature was permitted to fall below an "almost critical" fever level. Clearly hypothermia is contraindicated in pneumonia.

Further discussion of the literature on hypothermia is precluded by lack of space.

HYPERTHERMIA

Because of limitation in space this discussion will be restricted to a consideration of the therapeutic use of hyperthermia.

Since many of the dangers of hyperthermia treatment are believed to be the result of cerebral anoxia, several clinics have adopted the routine of oxygen administration. Looney & Borkovic (116), however, studying the arterial and internal jugular blood of patients receiving diathermy treatment for paresis, found only minor changes in the oxygen saturation of the arterial blood and in the arteriovenous oxygen difference. They concluded that the oxygen uptake of the brain was apparently adequate and that therefore oxygen administration was not warranted. Cullen, Weir & Cook (117) made a similar study of patients rendered hyperthermic by means of the Burdick cabinet. In agreement with Looney & Borkovic, they found that the arterial oxygen saturation percentage was not significantly reduced during the period of elevated temperature (105°F.), but that, when account was taken of the decreased carbon dioxide content and increased pH caused by hyperventilation, the oxygen partial pressure of the arterial blood could fall as much as 25 per cent, a reduction comparable to that resulting from an ascent to an elevation of 17,500 ft. If oxygen were administered throughout the period of treatment, although there was no marked increase in arterial oxygen saturation, the fall in carbon dioxide tension and the rise in pH were less marked than in patients not receiving oxygen, and accordingly the oxygen partial pressure rose. Administration of oxygen also reduced the incidence of restlessness, excitement, mental confusion, and tachycardia, which are attributable to cerebral anoxia.

Control of fluid and salt administration in hyperthermia treat-

ment guided by repeated determination of plasma specific gravity has aided in the prevention and handling of the collapse which tended to occur when the specific gravity rose ("dehydration") or fell ("overhydration") outside the normal limits of 1.0255 to 1.0290 (118). Both forms of collapse were accompanied by restlessness, mania, rapid pulse, nausea and vomiting, and decreasing urine and sweat output. When sweating is absent, determination of plasma specific gravity may be the only method of differentiating between the two states, and thus of avoiding the overloading of the body with salt and water which may occur if these signs lead one to mistake overhydration for dehydration. However, the low plasma specific gravity in the later stage of "overhydration collapse" should not be taken as evidence of a supernormal blood volume. It may rather be the result of loss of plasma protein into the tissue spaces. Such loss, coupled with the reduction in the albumin-globulin ratio reported by Kopp (119), would reduce the colloidal osmotic pressure of the plasma and permit a reduction of blood volume with subsequent collapse. The therapy indicated would not be fluid restriction, but rather plasma transfusion. Pruce (120) has reported what he considers to be the first case of shock developing after hyperthermia treatment successfully treated by the administration of plasma.

According to Edelman *et al.* (121) administration of adrenal cortical extract before and after hyperthermia treatment reduced fatigue and accelerated recovery. It prevented the fall in blood sugar which otherwise occurred regularly. In some cases it prevented or reduced the fall in plasma sodium, but had no effect on plasma potassium. It also caused reduction in the concentration of sodium in the sweat. However, the retention of sodium was insufficient to account for the clinical benefit of extract administration.

In infectious fevers the plasma ascorbic acid concentration is reduced. However, since this change is not produced by physical hyperthermia (four hours at 104°F.), dietary supplementation with vitamin C is not required as a part of the regimen of such treatment (122).

A newly recognized hazard of otherwise harmless hyperthermia treatment is the possibility of termination of early pregnancy (123). Only one of eighteen female rabbits, in which the body temperature was raised to 108° to 109°F. for twenty minutes

72 to 80 hours after mating, produced litters. Subsequently eight of ten of these animals produced normal litters, a fact showing that no permanent damage to the reproductive system resulted from the hyperthermia.

Kenny treatment of poliomyelitis.—The application of hot moist packs to the muscles in spasm in the acute stage of poliomyelitis is a cardinal feature of the Kenny treatment (124). Such treatment has been shown by the electromyographic studies of Schwartz & Bouman (125) to decrease the action potentials of the spastic muscles.

The mechanism whereby the relaxation is mediated is not understood. The muscle shortening, at least before contracture sets in, is a tetanus of central origin, since it is relaxed by spinal anesthesia (126). It is possible that the fomentation so alters discharge of the cutaneous receptors as reflexly to decrease the activity of the motoneurons responsible for the spasm. Wright (127) reports that the application of packs causes a diminution of the senses of touch and pain of the skin. She suggests that the resultant reduction in the number of afferent impulses reaching the central nervous system decreases the spasm, so permitting resumption of an adequate blood supply to the muscles. Tests of the strength of voluntary contraction of forearm flexors with and without Kenny packs applied to them showed a statistically significant reduction attributable to the packing, the magnitude of which (10 per cent) is so small as to be of questionable importance in relation to their clinical use in poliomyelitis (128).

The observations of Abramson *et al.* (129) that the blood flow through extremities with post-poliomyelitic paralysis is not subnormal led them to question the rationale of treatment directed toward increasing the blood flow. It is not clear, however, that the patients were in the acute stage of the disease. If they were not, the findings are not relevant to those features of the disease (including spasm) toward which the Kenny treatment is directed.

CONCLUDING COMMENTS

In retrospect, the chief contributions of the last few years in the field of this review appear to be those dealing with hypothermia. It has been shown that the tolerable range of low body temperature is much wider in mammals than formerly thought. This has afforded wider scope for the therapeutic use of cold. The

extent of this tolerance has provided something of a challenge to the homeostatic conception. A note of caution is warranted by the deleterious effect of lowering body temperature in experimental pneumonia. There have also been notable advances (largely unpublished) in techniques of protection against extreme cold and heat.

Looking forward, it is evident that cold will be a useful analytical tool, especially in situations where opposing processes have quite unlike temperature coefficients, so that the metabolic pattern can be altered by changing temperature. Also, the work on shock, immersion foot, and on tissue respiration all points toward increased appreciation of the importance of evaluating the fit of metabolism and the supply systems. Further investigation will surely be stimulated by the conception that, within limits, cold itself is not damaging; rather it permits metabolism to continue under adverse conditions.

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TISSUE WATER AND ELECTROLYTE

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The following review will deal largely with certain internal factors controlling the distribution of water and electrolyte within the body. This narrow point of view was chosen because metabolism of water so obviously involves almost every phase of life that some limitation must be set up. The choice of this field of water metabolism is justified by the fact that considerable new information has been obtained in the past ten years by tissue analyses for water and electrolyte. The interpretation of tissue analyses is based on the postulates concerning the factors controlling distribution of body water so ably developed twenty years ago in the classic paper of Gamble, Ross, and Tisdal. The literature examined covers 1940 to September, 1943, but certain older papers will be cited. Practically no continental literature was available to the reviewer.

Briefly, previous work has shown that a first approximation of the amount of extracellular water may be obtained from the ratio of total tissue chloride to the concentration of chloride in a serum ultrafiltrate. Sodium has been found definitely in larger quantities than can be contained in an ultrafiltrate of serum, i.e., (a) in bone as an integral part of the calcified material and amounting to about one-third that in extracellular fluid, (b) in muscle within the fibers in variable amounts but normally approximating one-tenth that in extracellular fluids. Testes, connective tissue, fat, kidneys, liver, and gastric mucosa contain considerable non-extracellular chloride, but the amounts are not large compared to the total extracellular chloride. The elaboration of these facts in recent work will first be discussed as far as possible with respect to individual tissues.

In examining tissue analyses certain facts must be kept in mind in comparing data from different laboratories. (a) In most cases concentrations must be expressed on a fat-free basis. (b) The unit of tissue analysis is apparently the solid and not the water since, when analyses are expressed per kilogram of tissue, investigators usually correct the data to a constant solid content. It would be simpler to express all analyses per hundred grams of fat-free solids

in the first place and only use kilograms when speaking of concentrations per kilogram of water. Ideally, it might be better to use some chemical unit of the cell which is known to be constant but such a substance is at present not recognized. At least total nitrogen cannot be used. Corrections for content of blood are probably important in heart and liver but do not assume significant amounts for most purposes in muscle and brain. Correction for connective tissue solids is appreciable but, so far, chiefly useful in gaining an accurate picture of the amount of solids in intracellular water rather than in understanding factors controlling distribution of tissue water and electrolyte. In pathological states this factor will have to be carefully assayed.

Muscle.—Boyle & Conway (1) developed theoretic equations based on an equilibrium taking account of osmotic, electric, and Donnan factors. The theory was tested by experiments on frog muscle. The equations predict the accumulation of potassium chloride and the distribution of the water of frog muscle soaked at 3°C. in mixtures of potassium chloride and sodium chloride. The equations assume free diffusibility of potassium and chloride and indiffusibility of the phosphate esters within the cells. The equations predict that chloride concentration within the cells equals potassium concentrations in extracellular water, that water concentration within the fibers varies inversely with sodium concentration in extracellular fluid, and that, when potassium chloride is added to Ringer's solution, potassium chloride is added to the contents of the cells without water. The theory does not take into account the presence of intracellular sodium nor the exchange of sodium for potassium within the cells. Dean (2) elaborates these equations assuming that there is the equivalent of a pump at the membrane which either removes sodium from the cells or adds potassium to the cells. The theoretic development leads to much the same predictions as Boyle and Conway's equations. Wilde (3) has tested the theory in rats subjected to nephrectomy and injection of solutions containing varying amounts of potassium. Measuring intracellular chloride by the difference between total muscle chloride and the chloride that could be present in extracellular space as measured by inulin or sucrose, one finds that a rise in serum potassium is accompanied by a corresponding rise in intracellular chloride. Water shifts likewise are compatible with Boyle and Con-

way's equations. As will be pointed out this theory seems to fit the analyses of mammalian muscle and hearts.

Boyle, Conway, Kane & O'Reilly (4) measured the diffusion space of frog muscle for inulin, chloride, sodium, and magnesium. From a consideration of the rates of diffusion, interstitial fluid is somewhat smaller than chloride space. Fisher & Subrahmaryan (5) find the glucose space is smaller than the chloride space. Conway & Fitzgerald (6) measured diffusion space of rabbit tissues with inulin, urea, and chloride. The inulin space is smaller than chloride space (9 and 15 per cent respectively). Dean (7) analyzed a single isolated fiber for chloride and thought all chloride was outside the fiber. In perfusion experiments Danielli (8) found hemoglobin was contained in about 5 per cent of frog muscle while chloride at the concentration of the perfusate would occupy 10 to 12 per cent of the space. The same author (9) found certain colloids affected the rate of edema formation according to their colloidal osmotic pressure (ovalbumin, hemoglobin, and acacia) while serum, erythrocytes, and platelets retard the rate; the effect is not related to the supply of oxygen. The retardation is thought to depend on some reaction with the endothelial lining of capillaries.

Factors affecting the accumulation or retention of potassium in mammalian muscle indicate that it is not primarily a metabolic process requiring continuous expenditure of large amounts of energy. Lyman (10) found radioactive potassium entered denervated muscle 2.86 times as fast as the intact muscle. This was explained as due to a change in permeability accompanying denervation. However, Noonan, Fenn & Haeghe (11) explained similar changes in stimulated and denervated frog muscle by changes in the circulation rate. Dean (12) found the rate of exchange of potassium was the same in the presence or absence of abundant oxygen as long as the muscle was functional. Iodoacetate increased the rate of potassium loss in the absence of oxygen but not in the presence of oxygen. Fenn, Koenemann & Sheridan (13) perfused frog legs with a solution containing red cells and acacia. The rate of loss of muscle potassium was the same when the solution was equilibrated with oxygen or nitrogen. Thus the evidence is that muscle potassium will be maintained as long as either anaerobic or aerobic metabolism is maintained.

Torda (14) found that calcium-free Ringer's solution retards the loss of muscle potassium in frogs and high concentrations of calcium accelerate the loss, the effect being reversible. Steinbach (15) showed that sodium can be exchanged with potassium in frog muscle and the effect is reversible.

Perhaps the most complete description of the chemical constitution of muscle is that presented by Manery, Danielson & Hastings (16). These authors develop the idea that the fibers are surrounded by an extracellular phase made up of the vascular system, blood, and connective tissue mixed with ultrafiltrate of plasma. Their analyses show that the chloride of connective tissue is so high in relation to sodium, that about 10 per cent of the connective tissue must be made up of cells containing potassium and chloride. In the calculation of the chemical constitution of muscle fibers, the correction for connective tissue is small with respect to chloride and potassium but considerable with respect to intracellular and extracellular solids. Muntwyler, Mellors, Mautz & Mangun (17) report a similar electrolyte pattern in the tendons of dogs but without as great an excess of chloride as was found in rabbits. Briefly, the analyses show per kilogram of fat-free dog tendon: water, 668 grams; sodium, 93 mM; potassium, 6.1 mM; chlorine 79 mM. This work showed that the composition of tendons varies like an ultrafiltrate when plasma concentrations are altered. Dog muscle contains about 4.9 gm. of collagen and 187 gm. of tissue excluding the muscle fibers, of which 85 per cent is water. The following values for extracellular water per hundred grams of fat-free solids of dog muscle indicate that the three methods of calculating extracellular water lead to approximately the same result: (a) the ratio of total chloride to the concentration of chloride in a serum ultrafiltrate gives 67 gm.; (b) the correction for the connective tissue by collagen determination gives 66 gm.; (c) the correction for intracellular chloride by an arbitrary constant (total chloride minus one, divided by chloride concentration in serum ultrafiltrate) gives 58.5 gm. Thus there is a small amount of chloride in connective tissue cells and probably a somewhat larger amount within the fibers. Furthermore, Drinker's work (18) would indicate that the capillaries let through variable amounts of plasma proteins so that the Donnan factor usually employed is too large since it assumes that interstitial fluid is free of plasma proteins. It is apparent that the volume of extracellular water is only measured as

a first approximation by the ratio of the chloride content to the concentration in a serum ultrafiltrate.

Wallace & Hastings (19) have applied a method of determining carbon dioxide to cat muscle. The data indicate that the muscle contains about 12 mM carbon dioxide per kilogram or about 10 mM per kilogram of intracellular water. This indicates that the pH of the cells is 6.93 ± 0.12 . When extracellular bicarbonate and pH are varied, the cellular bicarbonate decreases about 15 per cent. Assuming that the carbon dioxide pressure of serum measures the pressure of carbon dioxide within the cells, the change in cellular pH is negligible in acidosis but in alkalosis the pH becomes less within the cells when the serum bicarbonate is raised and pH increased in extracellular fluids. The intracellular bicarbonate is apparently but little altered by the concentration of bicarbonate in the environment but the intracellular pH is affected by the pressure of carbon dioxide. Yannet (20) using Danielson and Hastings' (21) method found no change in intracellular bicarbonate in alkalosis. He did not report the bicarbonate determinations because small changes in intracellular bicarbonate would not be revealed by his analyses. (The method was not giving as good checks as the originators were able to obtain.) Wallace & Lowry (22) soaked rat muscles in various solutions containing from 0 to 87 mM bicarbonate per liter. Intracellular bicarbonate did not show significant variations under these circumstances.

While the calculation of extracellular water from chloride is only a first approximation, useful deductions on factors controlling muscle water may be obtained by this method. The earlier work by Hastings & Eichelberger (23) indicated that increases in intracellular water accompany either an acidosis or alkalosis when no change in concentration of serum sodium is produced. Unfortunately, some of the experiments do not report muscle potassium so that it is not clear whether minor shifts in intracellular sodium and potassium explain these changes. Yannet & Darrow (24) applied statistical methods to analyses of tissues in experiments involving decreases in extracellular electrolyte which were permitted to persist about eighteen hours. The experiments did not induce large changes in the extracellular water of muscle so the changes in total water were chiefly intracellular. The direct correlation between muscle and serum chloride is such as to indicate that about 1 mM of chloride per one hundred grams of fat-free solids does not

react like an ultrafiltrate of plasma. This is about 15 per cent of the total muscle chloride. Presumably, this amount of chloride is intracellular and its magnitude is about the same as that predicted by Boyle and Conway's theory. In calculating extracellular water, the authors recommend subtracting 1 mM from the total chloride per one hundred grams of fat-free solids before dividing by the chloride concentration in extracellular fluid. At normal serum electrolyte concentrations, muscle water varies directly with muscle potassium and sodium—the former being an effect on intracellular water and the latter presumably chiefly extracellular. The effect of variations of potassium on muscle water is such as to suggest that potassium is lost with water at a concentration of about 200 mM per liter. This would indicate that a little less water is freed than would be deduced from the strict osmotic effect of potassium salts in water. Muscle water varies inversely with the concentration of sodium in serum, the increase in water representing a shift into the cells. The magnitude of the shift of water into the cells is only about two-thirds as great as would be obtained if the concentrations of univalent base showed relatively the same changes inside and outside of the cellular membranes. Mellors, Muntwyler & Mautz (25) report similar findings and extend the observations to experiments involving increased concentration of sodium in serum. They point out that the relationship is not precise, but it is, nevertheless, real and indicates that under many circumstances the apparent osmotic activity of potassium in muscle fibers decreases. Miller & Darrow (26) found that muscle potassium in rats is usually 47 to 49 mM per one hundred grams of fat-free solids but may drop to 44 as the result of various procedures such as, (a) the injection of potassium chloride if the rats are permitted to survive eighteen hours after the last injection, (b) injection of hypertonic sodium chloride plus sodium bicarbonate when the rats are permitted to survive eighteen hours, and (c) high potassium diet. These losses are unaccompanied by significant loss of total water or calculated changes in intracellular water per one hundred grams of fat-free muscle. Darrow & Sarason (27) found a similar decrease in muscle potassium in rats fasted or subjected to considerable reduction of atmospheric pressure. In the latter case voluntary fasting rather than anoxia was regarded as the apparent cause of this change. These decreases in muscle potassium are not accompanied by loss of nitrogen and are encoun-

tered when essentially normal concentrations of sodium, chloride, and potassium are present in serum. Thus the amount of potassium per unit of solids, nitrogen, and water can vary, the variation probably not exceeding 10 mM per kilogram of muscle (2.5 mM per one hundred grams of fat-free solids). Per kilogram of intracellular water, muscle potassium in rats apparently can vary from 146 to 160 mM while serum sodium is constant. This change does not apparently involve loss of intracellular sodium. The loss of muscle potassium probably involves no change in intracellular water (26) but this point is not adequately established since the data on normal cats suggest a direct relationship between total potassium and water (24).

The replacement of muscle potassium by sodium originally found by Heppel in rats fed a diet low in potassium has been produced by Miller & Darrow (26, 28) in rats fed a diet low in potassium and in rats receiving repeated injections of desoxycorticosterone acetate. Orent-Keiles & McCollum (29) also report similar tissue analyses on rats fed a diet low in potassium. Ferribee *et al.* (30) demonstrated similar changes in muscle of dogs in which they produced the syndrome resembling periodic paralysis and diabetes insipidus by the injection of desoxycorticosterone acetate. Miller & Darrow (26) showed that this intracellular sodium is readily replaced by injected potassium and that rats having a deficit of potassium show increased resistance to potassium poisoning. Heppel (31) showed that this intracellular sodium is in rapid diffusion equilibrium with radioactive sodium. Depletion of muscle potassium can also be produced by cortical extract (28) and estradiol benzoate and testosterone propionate (32). Conditions associated with low concentration of potassium in serum are probably necessary to produce this loss of intracellular potassium and increase in intracellular sodium.

The potential reservoir for potassium in animals depleted of muscle potassium explains the increased period of survival of rats receiving desoxycorticosterone acetate before nephrectomy or bilateral ureteral ligation (33, 34).

When serum potassium in rats is raised by the injection of potassium salts, muscle potassium rises quickly to 50 or 53 mM per one hundred grams of fat-free solids but returns within ninety minutes to normal (26). Eichelberger (35) did not obtain a rise in muscle potassium after waiting over an hour after the injection of

potassium bicarbonate in dogs. The apparent intracellular sodium decreases when the muscle potassium is abnormally high. In these experiments the concentration of serum sodium does not show great variations and yet the calculated intracellular water likewise does not show great variations despite a fairly great increase in intracellular potassium concentration. The theory of Boyle & Conway explains these findings since according to their calculations a rise in serum potassium leads to a shift of potassium chloride into the fibers without water when the concentration of serum sodium is constant. It would also explain the apparent loss of intracellular sodium for the correction for intracellular chloride becomes larger under these circumstances. The same phenomena are exhibited by rats suffering from advanced adrenal insufficiency for their muscle has a high potassium content without a corresponding increase in total water (36). Recently high muscle potassium has been found in adrenal insufficiency in dogs by Muntwyler, Mellors, Mautz & Mangun (37) and Buell & Turner (38). The values for normal potassium are somewhat low in the former paper. In the latter they are so high and so at variance with previous values, that it seems probable some error occurred in the methods. Muscle potassium becomes abnormally high only during conditions associated with a rise in serum potassium. Most workers on adrenal insufficiency agree that the rise in muscle potassium is not the explanation of the muscular weakness but a more or less physiological reaction to the rise in concentration of serum potassium. Indeed, the reviewer has unpublished data on rats with chronic adrenal insufficiency which show low muscle potassium while on a diet low in potassium. The evidence seems clear, therefore, that the rise in muscle potassium is not a direct effect of lack of the hormone on the muscle but an indirect result of renal failure leading to retention of potassium and depletion of extracellular electrolyte.

Miller (39) has called attention to variations in muscle potassium that occur in rats subjected to depletion of extracellular electrolyte, scalding, hemorrhage, and injections of epinephrine. In some of these experiments potassium rises to 50 or 53 mM per one hundred grams of fat-free solids while the serum potassium also rises to 5 or 10 mM per liter. Since no source for potassium adequate to explain the changes can be found elsewhere in the body, Miller postulates loss of muscle solids without immediate loss of muscle potassium. The changes in muscle glycogen do not explain

the findings and the nature of lost solids is unexplained. The findings suggest an explanation of the rise of serum potassium seen in shock. This effect must also be taken into account in addition to the evidence that the potassium comes from the liver after injections of epinephrine (40).

Wood, Collins & Moe (41) measured the arteriovenous differences in the stimulated muscle of a heart-lung preparation. Loss of potassium and increase in water is confirmed. The loss of potassium is immediately reversed when stimulation ceases but recovery of normal water content is a slow process. The change is dependent on intact nerve endings in the curare treated muscle. Miller & Darrow (42) found muscle composition remained relatively constant with exhausting exercise in the intact rat but muscle potassium rose in the muscles previously depleted of potassium by injections of desoxycorticosterone acetate. The ability to react to electrical stimulation (43) or exercise (42) was not affected by fairly wide variations in muscle potassium. Under certain circumstances (44) injections of potassium chloride delay the fatigue of stimulated muscle. Thus while loss of potassium may be a normal phenomenon of contraction, the ability to resume normal concentration of electrolyte within the fibers is quite efficient and prompt.

Darrow & Sarason (27) studied the composition of muscle and liver of rats exposed to low atmospheric pressures. Before the exposure some of the rats were depleted of body potassium by diets low in potassium and others by the injection of desoxycorticosterone acetate. After exposure, some of the rats showed increase in intracellular sodium without demonstrable loss of potassium. This effect is exaggerated in rats receiving desoxycorticosterone and is apparently an effect of low atmospheric pressure.

Eichelberger and coworkers have applied the technique of tissue analyses to various conditions in dogs. During pregnancy there is no change in muscle except increase in blood content (45). With a single hydronephrotic kidney (46, 47), the muscle does not differ significantly from the control but with double hydronephrotic kidneys, intracellular water is decreased and extracellular water increased. The decrease in intracellular water is accompanied by a decrease in muscle potassium. The injection of an isotonic solution of sodium chloride and sodium bicarbonate produced no change in the intracellular phase although there was an increase in the volume of extracellular water. The injection of both

types of dogs with an isotonic solution containing sodium chloride and potassium bicarbonate produced slight increases in intracellular water per unit of fat-free solids. In all cases there is evidence of displacement of intracellular sodium by potassium, the rise in potassium being considerable in the dogs with double hydro-nephrosis in which the initial potassium was abnormally low. In experimental hypertension (48) there is little change in the muscle except an increase in extracellular water.

The composition of muscle in dietary muscular atrophy is reported in rabbits by Morgulis & Osheroff (49) and Fenn & Goettsch (50). Both studies demonstrate increase in sodium and chloride and decrease in potassium. The changes are chiefly explainable by increase in extracellular water but the figures also suggest some displacement of potassium by sodium within the fibers.

The analyses of dolphin muscle (*Tursiops truncatus*) indicate that it resembles other mammalian muscle (51).

Heart.—The analyses of the heart cannot, at present, be interpreted in osmotic terms. When decreases in extracellular electrolyte are produced (24), heart chloride varies directly with the concentration of serum chloride, apparently all chloride being in diffusion equilibrium with plasma chloride. However, heart sodium varies directly with serum sodium so as to indicate a considerable amount of intracellular sodium. Surprisingly, no relation can be demonstrated between tissue water and any of the obvious factors interpretable in simple osmotic forms. Water does not show an inverse relationship to the concentration of serum sodium nor is there a correlation between the concentration of serum sodium and univalent base in heart water. In studying the composition of cat heart following the injection of potassium salts (52), it was found that heart potassium was usually about 40 mM per one hundred grams of fat-free solids but could rise quickly to 48 mM following injections of potassium salts. With the rise in serum potassium, the data show the appearance of considerable amounts of intracellular chloride. Although the heart potassium is related to serum potassium, there is no evidence that heart block is caused by the high muscle potassium *per se* since heart block is correlated with the level of serum potassium. The findings in this study as well as others suggest that heart potassium is more variable than muscle potassium (38 to 48 mM per 100 grams of fat-free heart solids in cats). The usual finding is at the lower range (40 ± 0.7

mM). Furthermore, there is evidence of reciprocal changes between muscle potassium and sodium. More precise studies will be needed to demonstrate the relation of the changes in heart sodium and potassium to heart water but if the wide variation in muscle potassium can be shown to be unassociated with change in intracellular water, the lack of a correlation between the concentration of serum sodium and heart water or concentration of univalent cations in heart water would be explained.

A series of papers from Hastings' laboratory gives analyses of rat hearts at various ages (53, 54, 55). During growth, there is a decrease in extracellular water largely explainable by growth of the muscle fibers. With old age, extracellular water increases owing to some decrease in fibers. Dietary retardation of growth slows up these changes. The apparent concentrations within the cells are surprisingly constant. Lowry, Gilligan & Hastings (56) found that, following temporary ligation of a branch of the coronary artery of dogs, the injured muscle shows increase in extracellular water as evidenced by rises in chloride, sodium, and water. Hitchings, Daus & Wearn (57) studied the process of cardiac hypertrophy following the production of aortic insufficiency in rabbits. During the initial phase there is increase in extracellular water. Later the fibers increase and the heart assumes a normal composition. Wood & Moe (58) demonstrate that digitalis glucosides produce displacement of intracellular heart potassium by sodium, the change being definite with therapeutic doses, and greater with toxic doses. The effect is unaccompanied by shifts of water from the fibers and seems to be related to the therapeutic action.

It is somewhat difficult to demonstrate decrease in heart potassium as a result of diets low in potassium or the injection of desoxycorticosterone acetate but this occurs (28, 29) and probably is a factor in producing the cardiac dysfunction and necrosis seen in these conditions.

Liver.—The changes in liver water and electrolyte are chiefly those associated with changes in its organic constitution. The data of Fenn & Haeghe (59, 60) bring this out most clearly. In cat livers one gram of glycogen is deposited with 1.46 ± 0.209 gm. of water, one gram of protein with 3.58 ± 0.107 gm. of water, and one gram of lipid with 0.125 ± 0.03 gm. of water. In the case of glycogen a small amount of chloride that is considered extracellular also accompanies glycogen deposits. With increase in glycogen, liver po-

potassium remains constant per unit of fat-free solids. The glycogen is apparently added with water and potassium within the cells, together with a small amount of extracellular fluid so as to increase the total amount of liver. McBride, Guest & Scott (61) present a different interpretation. They point out that nonglycogen solids change with deposit of glycogen. Their data do not give a sufficient number of fat analyses for adequate interpretation. Nevertheless, it is true that glycogen plus protein does not account for a constant proportion of fat-free solids. From this point of view the relation of solids to water has not been adequately worked out and Fenn and Haeghe's correlations are partly fortuitous in that they are accompanied by changes in unidentified solids other than fat, protein, and glycogen. When there is no change in the glycogen-free solids, 2.7 gm. of water are deposited with one gram of glycogen. Fenn's work indicates that the amount of potassium is relatively constant per unit of fat-free solids.

It is not certain that one can evaluate liver analyses without glycogen, as well as fat determinations. Usually there are in the liver as many or more equivalents of chloride as there are of sodium. This relative excess of chloride is variable and indicates that variable amounts of intracellular chloride can be found in the liver (24). Since most of the chloride is extracellular, this finding is not incompatible with the work of Truax (62) who finds the chloride space is equal to the anatomically measured extracellular space. Some sodium is also not extracellular since there is no correlation between the liver sodium and the concentration of sodium in serum. If sodium were exclusively extracellular, this could only occur if increases in extracellular water always accompanied decreases in the concentration of sodium in serum. There is evidence of shift of water into the cells with the decrease in the concentration of sodium in serum, the change being about one-half that which would keep the relative changes in concentration of univalent base in the liver the same as that in serum. Eichelberger (35) demonstrated that the total water increased in livers of dogs receiving injections of isotonic sodium chloride plus potassium bicarbonate. The changes involve both intracellular and extracellular water and are accompanied by accumulation of potassium. Excepting the over-all enlargement, Darrow & Sarason (27) found no changes in electrolyte and water at low atmospheric pressure that were not referable to fasting.

Brain.—The work of Wallace & Brodie (63) fits in with previous work indicating a peculiar barrier between blood and brain when compared to that of other tissues. By studying the equilibrium concentrations of chloride, bromide, and iodide in brain, spinal fluid, and plasma, interesting relationships are revealed. First, when bromide or iodide is put in the cisterna, it rapidly enters the blood but never attains high values in the ventricles or in fluid collected over the cortex. On the other hand, when iodide or bromide is injected into the blood, the displacement of chloride by these ions is the same in all parts of the cerebrospinal fluid and all parts of the central nervous system. This would indicate that the ionic constitution of the interstitial fluid of the brain is not dependent on peculiar properties of the choroid plexus but on some function of the blood-brain barrier. However, the choroid plexus apparently furnishes the ventricles with fluid having the same make-up but of itself does not determine the constitution of the interstitial fluid of the brain. In this sense cerebrospinal fluid may be considered to illustrate but not determine the composition of the interstitial fluid of the brain.

Weir (64) showed that the ratio of the cerebrospinal fluid bromide to serum bromide becomes higher when serum bromide is higher. The varying ratio is incompatible with simple assumptions of membrane permeability. Certain previous work receives new reinterpretations in the light of the findings of Wallace & Brodie. Amberson, Nash, Mulder & Binns (65) found little change in chloride of the brain when serum chloride was displaced by sulphate. Yannet (20) had a similar experience in alkalosis in which serum chloride was displaced by bicarbonate in the serum. However, when both serum chloride and sodium were reduced (66) brain chloride showed a direct relationship with serum chloride. Probably the chloride concentration of spinal fluid and the brain only varies directly with that in serum when sodium shows a similar variation. All work indicates that the equilibrium between the extracellular constituents of the brain and plasma are only reached after longer intervals than in other tissues.

Since new work involving complete analyses for tissue electrolyte is not at hand, this field is ripe for investigation. Not only is there the challenge of the peculiar blood-brain barrier but also the loss of potassium from the brain cells apparently in response to decrease in concentration of sodium in serum which minimizes

the exchange of water between extra- and intracellular fluids (66).

Other tissues.—Little work has been done recently on other tissues. Eichelberger & Bibler (67) report analyses of normal and nephrotic kidneys of dogs. The concentration of sodium plus potassium in kidney water is 210 mM per liter of water. If chloride concentration measures extracellular fluid, the concentration of univalent base in nonextracellular fluid is 253. It seems likely that even allowing for tubular urine, some chloride must be intracellular.

Haldi, Giddings & Wynn (68) point out that the variations in the water content of the skins of rats on different diets and in the two sexes are explainable on the assumption that fat is added to skin of relatively constant content of water and protein.

Clarke (69) studied the changes in size of the sexual skin of baboons. The swelling during the estrus cycle involves a deposit of water and protein together with sodium and chloride. Part of this fluid and electrolyte is derived by transfer from the rest of the body.

Wills (70) describes changes in the secretion and composition of the salivary glands in response to pilocarpine and electrical stimulation of the nerve. The glands do osmotic work by abstracting water and potassium.

Talbot, Lowry & Astwood (71) report the changes in the uteri of rats after injections of estradiol. At first there is a rapid increase in water, chloride, and sodium while potassium and phosphorus increase more slowly. The concentration of sodium plus potassium remains fairly constant per unit of water but more is contributed by sodium during this early part of the response. At first the ratio of potassium to phosphorus increases but later assumes the usual value. Before and at the completion of the response, chloride is too high relative to sodium to be contained in the same volume of extracellular fluid as sodium, though during rapid growth the ratio of the two concentrations is the same as in serum. The data indicate that rat uteri contain intracellular chloride.

Studies of synovial fluid indicate that it has the chief characteristics of a filtrate of plasma but modified by the content of a peculiar protein (72, 73, 74).

Studies are reported on the permeability of various placentae to radioactive sodium (75 to 79). The permeability varies with the stage of the gestation and the type of placenta. The more rapid

the rate of growth of the fetus, the more rapid is the exchange of sodium.

In the guinea pig 73 per cent of the water of the plasma is exchanged each minute when deuterium oxide is injected intravenously. The deuterium oxide comes into equilibrium with about 65 per cent of the body weight (80). This study illustrates the rapidity of water exchange throughout the body.

The recent book by Drinker & Yoffey (18) makes it unnecessary to review the work on the composition of lymph. Attention should be directed, however, to the fact that cardiac, liver, and lung lymph has been demonstrated to contain large amounts of plasma proteins (2 to 4 per cent) and this is thought to reflect large amounts of protein in the interstitial fluids.

Depending on the mode of administration, Noonan, Fenn & Haeghe (81) found radioactive potassium at greater relative concentration in liver and intestines of rats than in other tissues. The experiments involved raising the serum concentration of potassium about 2 mM and indicated a mass movement of excess potassium into these organs. To a lesser extent the kidneys and heart showed the same phenomenon. While certain experiments indicated that this was dependent on the blood supply exposing these organs to greater concentrations of potassium, later experiments in rabbits and rats (82) indicated that these organs removed excess potassium and only released it gradually to the muscles.

Measurement of extracellular water.—Greenberg, Campbell & Murayama (83) found that radioactive sodium quickly attains equilibrium with about 24 per cent of the body water, distributing itself like total body sodium (bones not studied). Manery & Bale (84) give more complete data on rabbits including total chloride and sodium as well as radioactive sodium. After twenty-four hours, radioactive sodium is distributed in the same relative proportions as total sodium; the penetration is rapid in extracellular fluids but somewhat slower in intracellular fluids. From the concentrations of radioactive sodium, extracellular fluid is about 29 per cent of the body weight. Brain and testes reach equilibrium at a very slow rate. Manery & Haeghe (85) made similar studies with radioactive chloride. Penetration was rapid and complete in the kidneys, liver, muscle, cartilage, and tendon, but was not complete within an hour in the testes and gastric mucosa. In the latter the space entered equalled the space entered by radioactive sodium. Only a

trace entered the brain within an hour. Radioactive chloride does not come into complete equilibrium with tissue chloride within an hour.

Winkler, Elkinton & Eisenman (86) have compared the apparent volumes of distribution of radioactive sodium, radioactive chloride, and thiocyanate in intact dogs subjected to deprivation from water as well as in an adrenalectomized dog before and after treatment. The volumes of distribution are least for chloride, intermediate for sodium, and largest for thiocyanate. Yet the changes in volume in successive determinations are comparable. Elkinton & Taffel (87) give data suggesting that a considerable and variable amount of thiocyanate becomes intracellular. Lands, Cutting & Larson (88) found that the thiocyanate and chloride volumes of the various tissues of cats are approximately the same but neither ion is strictly confined to extracellular fluids. Chloride is distributed in a larger volume than thiocyanate according to these data. Kaltreider, Meneely, Allen & Bale (89) have critically examined the thiocyanate and radioactive sodium methods of measuring extracellular water. They show that the diffusion into large transudates is sufficiently slow to require over nine hours for equilibrium and that the radioactive sodium comes to approximate equilibrium with nonextracellular sodium of bones within three to four hours. The correction for the known non-extracellular sodium in muscles and bones is, therefore, about 20 per cent of the value as usually measured. In man the thiocyanate method is subject to errors, leading to values considerably higher than the true extracellular water. Ashworth, Muirhead, Thomas & Hill (90) recommend a dose of 25 mg. of thiocyanate per kilogram and a correction for rate of disappearance. Redeterminations check within 6 per cent. Bromide is distributed in a volume of fluid approximating extracellular fluid (91). Radioactive chloride constitutes the best of the present methods of measuring extracellular volume but its short half life makes its use impractical. While relative changes in extracellular volume may be evaluated by present methods absolute values are probably not measured. In normal adults extracellular water is approximately 20 per cent of the body weight. Probably balance of chloride together with serum concentrations will prove the most reliable method of following changes in extracellular volume.

Variations in extracellular volume.—Injection of concentrated plasma increases plasma and thiocyanate volumes in dogs. The latter change is not accounted for by the amount of salt injected and would not be expected from the studies by tissue analysis. (92).

Flemister (93) measured the thiocyanate and water concentration in various tissues of rabbits before and after increasing and decreasing body water without comparable changes in extracellular electrolytes. Considering the thiocyanate concentrations as measures of extracellular water, intracellular water is little changed by these procedures. The volumes of extracellular water in skin and muscle constitute two-thirds of the total; plasma volumes remain relatively constant while skin volumes fluctuate in either direction. Lands, Cutting & Larson (88) measured chloride concentrations and thiocyanate volumes after infusions of 1 per cent sodium chloride and 5 per cent glucose. Extracellular volumes are increased by these procedures. Healthy women receiving continuous infusions after gynecological operations were studied by Stewart & Rourke (94). Balances of sodium, chloride, and potassium are given together with thiocyanate volumes. The large saline infusions over a period of two to four days increased the thiocyanate volumes about 80 per cent. Because of the tendency of thiocyanate to enter cells, these figures do not establish a corresponding increase in extracellular water. The glucose infusions lead to reductions in extracellular volumes owing to loss of sodium and chloride. During saline infusion (case of R.H.) potassium is lost and, relative to their respective concentrations in serum, more sodium than chloride retained. The relative excess retention of sodium equals the excretion of potassium and presumably represents exchange of potassium for sodium in muscle fibers.

Balance studies of tissue water and electrolyte.—As illustrated in the previous paragraphs the composition of normal tissue water and electrolyte is fairly well known and a good deal of information is available which shows the changes which may be expected in pathological states. In drawing conclusions about changes in tissue water and electrolyte from balance experiments, the muscle is quantitatively the most important intracellular compartment and hence it seems justified to examine balance experiments in the light

of what is known to occur in muscle. In this respect, the work of Gordon *et al.* (95) is a model since it shows that over comparatively long periods of growth the body takes on the composition which tissue analyses have established.

Elkinton & Taffel (96) subjected dogs to complete deprivation of water and food. This procedure leads to extremely high concentrations of sodium in serum. In other experiments (97) dogs received intravenous injections by hypertonic salt solutions or were subjected to procedures leading to depletion of extracellular electrolyte. From balances of sodium, chloride, potassium, water, and nitrogen, a system of calculation of changes in intracellular water is set up. The calculations are based on (a) osmotic shifts of water expected from changes in concentrations of serum sodium, (b) the loss of cellular water accompanying losses of nitrogen and potassium, and (c) the losses of cellular water due to losses of potassium without nitrogen. The expected concentrations of sodium in serum may also be calculated from the balances of water and univalent base together with an assumed initial value for total extracellular and intracellular sodium and potassium. Such calculation shows that some osmotic changes must take place within the cells making more water available particularly when extracellular electrolyte is lost. A number of the procedures in these experiments lead to loss of potassium unaccompanied by loss of nitrogen. The data indicate that this loss of potassium not accompanied by nitrogen attains but does not exceed the amounts that might be accounted for by the known variations in muscle composition revealed by tissue analyses under analogous conditions (26). In some experiments there is evidence of loss of potassium which is displaced by sodium, though this is the exception. When injection of sodium chloride without water leads to death, the manner of death suggests respiratory paralysis and no evidence of circulatory failure is obtained (98).

Rosenbaum (99) obtained balances in humans under conditions leading to changes in carbon dioxide and bicarbonate. In general the data indicate that changes in carbon dioxide take place throughout all body water while bicarbonate changes are confined to extracellular fluids.

Remington, Parkins & Hays (100) found losses of water and potassium following depletion of extracellular electrolyte. Since

nitrogen was not estimated, the data are difficult to evaluate and contribute little new. Swann, Collins, Cline & Dernehl (101) show that low oxygen pressure and low atmospheric pressure lead to greater losses of water than fasting but factors for further evaluation are not available. Sunderman & Dohan (102) report the plasma volumes, thiocyanate volumes as well as concentrations of serum components in dogs before and during diabetic ketosis. The changes are compared to fasting controls. Thiocyanate and plasma volumes per unit of weight are greater than in the controls. As measured by thiocyanate volume there is not as great a loss of sodium and chloride during the development of diabetic ketosis as during fasting. This finding would not be anticipated and should be checked by measurement of extracellular water by some method not subject to such gross errors as is the thiocyanate method.

Talbot, Butler & MacLachlan (103) report urinary excretions of nitrogen and electrolyte in an addisonian patient during three hundred days on various regimes. A retention of potassium in addition to nitrogen in response to testosterone is demonstrated. Strikingly low concentrations of serum potassium develop during testosterone administration. There are certain discrepancies with respect to the relation of nitrogen, potassium, and water balances to each other which cannot be completely explained but in no case are these discrepancies beyond those that might be expected from variations in muscle composition, especially when muscle potassium is replaced by sodium as would be the case as a result of therapy with desoxycorticosterone. The data indicate that storage of nitrogen may lower extracellular potassium under certain circumstances.

In a case of Cushing's syndrome (104), low serum chloride, low potassium, and high bicarbonate were relieved by administration of potassium salts. Since low serum chloride and high or normal serum sodium accompany diets low in potassium or following injections of desoxycorticosterone acetate, this work suggests that deficit of potassium is a feature of Cushing's syndrome and explains the findings in the serum. Hyperadrenalism could cause the development of deficit of potassium and lead to muscular weakness. The reviewer is convinced that deficit of potassium occurs in other clinical conditions and that unexplained high bi-

carbonate, low chloride, and low potassium in serum may be the findings that will lead to the discovery of these cases.

Fluid balance and adrenal insufficiency.—When an addisonian patient was restricted as to water intake while receiving sodium chloride (105), adverse symptoms developed despite a relative retention of sodium chloride and the development of more normal serum concentrations of sodium and chloride. When water intake was increased, symptoms did not develop despite increased excretion of sodium and chloride. In the former experiment, plasma volume decreased while it remained unchanged in the latter. Adrenalectomized rats receiving sodium chloride (106) do not survive a period of fasting any better than adrenalectomized rats receiving no sodium chloride. These experiments give further evidence that adrenal insufficiency is not simply a matter of water and electrolyte balance.

Fluid changes in shock.—Only a few references in this field can be cited. In traumatic shock, the concentration of serum potassium of dogs may rise terminally to 10 or 12 mM per liter (107). The injured muscles of the dogs in these experiments show loss of potassium but since sodium analyses were not undertaken, the type of change in the fibers cannot be adequately evaluated. Analyses of muscle, heart, liver, and pancreas are reported in experimental shock and adrenal insufficiency (108) but since fat was not determined, comparisons with the controls cannot be accepted at their face value. The findings are of interest since they suggest that liver potassium and phosphorus may be low in shock. Thus injured muscle and liver are possible sources for the potassium causing the rise in serum potassium in shock in addition to the change in untraumatized muscle cited earlier in this review (38).

Following bleeding (109, 110), plasma proteins drop in concentration owing to dilution, but albumin shows an absolute increase within six hours but does not attain normal values within a week. Globulin is regenerated more rapidly. When fluid intake is restricted before a severe hemorrhage, dogs are unable to dilute their blood and shock is more severe than in controls (111). When hemodilution occurs, proteins are added to the plasma and when hemoconcentration develops, plasma proteins are lost. In experimental shock produced by circulatory occlusion (112, 113) prevention of fluid loss by bandages is beneficial. These studies

confirm the importance of maintenance of plasma volume in shock and illustrate that in recovery from shock addition of serum proteins is a normal physiological occurrence as well as therapeutic measure.

As has been recognized for years, loss of extracellular electrolyte leads to decrease in extracellular water and plasma volume. These findings are thought to explain the picture of shock and susceptibility to shock accompanying loss of sodium and chloride. Recent work (114) demonstrates the reverse, i. e., large extracellular volume supporting plasma volume. Dogs were subjected to vascular occlusion of the legs for six hours and then received large continuous infusions of saline—amounts equivalent to as much or more than the body weight were given in three to eleven hours. Eventually, massive edema and stabilization of the blood volume developed and recovery occurred.

The role of adrenocortical compounds in shock is not clear. In adrenalectomized dogs (115, 116, 117) desoxycorticosterone acetate protects against the shock accompanying bleeding, loss of extracellular electrolytes, and injection of epinephrine but not against that following intestinal stripping or bilateral adrenalectomy. However, desoxycorticosterone is effective in the shock following one-stage adrenalectomy if the splanchnic nerves are blocked. The investigators believe desoxycorticosterone is of value to adrenalectomized dogs in maintaining plasma volume and electrolyte balance but not when the gluconeogenic function of the adrenal cortex is required.

In intact rats, shock produced by occlusion of the circulation was not benefited by cortical extract, compound E, corticosterone, or desoxycorticosterone acetate (118, 119). Prophylactic injections of desoxycorticosterone gave slightly favorable results in the shock following venous occlusion (120). Administration of cortical extract gave a somewhat higher incidence of survival while paradrine increased the death rate in shock following venous occlusion (121).

Plasma or blood transfusions induce a rapidly appearing edema when given during a mild crisis in adrenalectomized dogs. Injections of desoxycorticosterone or cortical extract will both prevent and cure this condition. While low blood pressure is usually present, it is not an essential feature of the phenomenon (122).

Intravenous plasma has again been found superior to intravenous saline in the treatment of traumatic shock (123). In a type of shock accompanied by evidences of vascular injury (guanidine intoxication), subcutaneous saline was superior to slow intravenous infusions but plasma infusions are required for the best results (124). Using serum protein concentrations as a guide to therapy untoward results were attributed to blood transfusions in the treatment of infantile diarrhea (125). This conclusion hardly seems justified in view of previous clinical and experimental evidence of benefit from transfusions in various type of shock.

As has been previously observed, babies suffering from diarrhea frequently develop high serum chloride and low serum bicarbonate following treatment with saline solutions (126, 127). Albridge concludes that saline solutions should not be used routinely in large quantities in babies suffering from diarrhea. This conclusion is only partly justified since use of a balanced solution containing sodium bicarbonate or sodium lactate will attain the beneficial effects of replacement of the deficit of sodium and chloride without aggravating the acidosis. This work calls attention to the fact that babies do not adjust serum electrolyte concentration very well unless able to form large volumes of urine. In dogs the optimal concentration for intravenous infusion has been systematically studied (128). A 0.4 to 0.6 per cent solution gives the greatest diuresis; a 0.2 per cent solution gives the least change in balance of sodium chloride. The authors believe that a solution containing two grams of sodium chloride per liter is as much as can be handled by humans receiving large infusions.

Attention has been directed to peculiarities in renal function of babies which limit the ability of infants to maintain fluid and electrolyte balance (129 to 132). Infants, especially newborn and premature ones, have low urea clearances which are not explainable by low rates of water excretion. With low rates of water excretion, the urea clearance is even more reduced. The phenomena are apparently related to a low inulin clearance. When serum chloride is high, urine chloride tends to be lower than in adults. The same is true for sodium and potassium. During dehydration no evidence of disturbance of urinary excretion could be found which is not explainable by the decreased rate of inulin and urea clearances that may be found in normal babies with similar urine

volumes. Practically, the work indicates that the protective action of babies' kidneys in controlling changes in concentration of serum electrolytes and in excreting urea requires relatively large volumes of urine and is less effective than that of adults. During the first year of life renal function gradually approaches adult standards.

Attention is again directed to the fact that deprivation from water leads to relatively mild disturbances compared to those accompanying loss of extracellular electrolyte (133). The latter leads to loss of plasma volume and is the prototype of the usual clinical conditions called dehydration.

Summary.—This review reveals that, like other constituents of the body, water is in a dynamic state in which all body water is being constantly exchanged. In a sense, there is no intracellular or extracellular water, for water in a particular phase is being constantly shifted and the amount in a particular location is controlled by many factors. Among these is the distribution of sodium and potassium. These ions are also in a dynamic state in which no part of the body is inaccessible to them. The reviewer has avoided problems of changes in membrane permeability since they require physiochemical treatment and at present contribute little to the interpretation of the distribution of body water and electrolyte. Although changes in the properties and activities of cytoplasm probably explain many of the changes in distribution of body water, at present data are not available which permit a description in these terms. The least we can do is to cease speaking of the distribution of various ions as if they were always excluded from certain phases of body water. The study of the changes in body water must take into account the fact that there are variations in the amount of sodium, chloride, and potassium in intracellular as well as extracellular fluids and a simple type of osmotic relationship does not describe the behavior of body fluids.

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ENERGY METABOLISM

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TWO CENTENARIES AND TWO WISHES

Just a century ago Joule (1) measured the mechanical equivalent of heat. A little earlier a young physician, Robert Mayer, had sent an article to the editor of a journal of physics and received no answer, had stormed into the study of a professor of physics to demonstrate that water could be heated by mere shaking (2), and had finally succeeded in publishing his thesis on the conservation of energy in the *Annalen* of Wöhler & Liebig (3).

Six decades before, Lavoisier & Laplace (4) had demonstrated that animal heat is derived from the oxidation of organic substances in the animal body. Some passages of their text suggest, in fact, that they already applied in their reasoning the principle of conservation of energy, even though they did not clearly formulate this principle and erred in some details. (They thought, apparently, that the heat from the production of a certain amount of carbon dioxide, "fixed air," was constant.) Lavoisier's contribution to physiology has been appraised by Richet (5).

In 1894 Rubner (6) published the results of his respiration calorimetry with dogs, proving Lavoisier's theory of the source of animal heat, and within a decade, after years of painstaking preparation, Atwater & Benedict (7) demonstrated that the law of conservation of energy is valid in working human beings.

The phase of establishing energetics in biology is therefore past. The concept of energy is taken for granted in biological research—so much so, indeed, that it is sometimes used with insufficient care. Expressions such as "energy production" or "energy-producing nutriment," rather common in biological papers, would probably have shocked the scientists of a century ago. They would surely have been bothered by the following passage (in one of the papers reviewed this year): "dividing the heat of the mechanical work done by the excess energy caused by this work." A specialist of course understands that the author just quoted means "dividing the heat equivalent of the work by the increase in energy metabolism related to this work." What is really

meant by "energy producing nutriment" is more difficult to decide. It probably means nutriment as a source of energy, in distinction to nutriment as a source of particular chemical compounds. Aside from promoting loose thinking in students, self-contradictory terms may not do much real harm. Still, during the centenary of the energy principle, we may well resolve to guard this principle against insults; its dignity is at least as important as a certain spelling or similar useful standardization.—This is the first centenary wish.

The best tool can be misused. Biologists have sometimes applied the energy principle where it should not be applied. That happened also this year when Adolph (8) in a book rich in valuable information and ideas wrote as follows: "That heat gain (in animals) in the long run equals heat loss may be regarded as a prediction of the first and second 'laws' of energy." The heat content in adult homeotherms remains constant in the long run when they keep their body weight and their body temperature constant. Neither of these regulations, however, can be predicted by the law of conservation of energy. The heat content of a cold-blooded animal is changed by a change in its body temperature; that of a growing animal or a woman in childbirth by a change in heat-capacity; yet these changes in no way contradict the law of conservation of energy, nor is the second law involved in this conservation problem.

A second centenary in bioenergetics is slightly over-due. In 1839 Sarrus & Rameaux (9) sent to the (at that time) Royal Academy of France a paper in which they deduced, mainly from mathematical and philosophical considerations, that the rate of heat production of large and small animals should be in proportion to the square of their respective linear dimensions. That was the beginning of the surface law of animal metabolism.

Whereas some biologists apply the law of conservation of energy too loosely, others (or perhaps the same ones) insist in an accuracy of the surface law that is unwarranted, to say the least. In investigating the heat exchange between animals and their environment one is justified in estimating a "true" surface when the conductivity of their surface layers, the emissivity of their surface, and similar factors are measured under suitable conditions. As a general standard unit of reference for the metabolic rate, however, the "true surface" is unsuitable; surface, for this general purpose, is not well enough defined, and every laboratory can use its

own private surface. Some authors use terms that make it impossible or at least discouragingly tedious to compare their results with those of other workers.

In ten papers (from eight laboratories) studied for this review metabolic rates of rats are expressed per unit of the surface area. Four of the ten authors did not state how they measured or calculated this area. One multiplied the $2/3$ power of body weight (in kg.) by 7.42, another by 9.1, a third by 10, to calculate the surface area in square decimeters. One author multiplied the $3/5$ power of body weight by 12.44, and two have calculated a new surface-weight relationship, presumably by an intricate logarithmic interpolation between three older ones ($7.42 W^{2/3}$, $11.36 W^{2/3}$, $12.44 W^{3/5}$). The new formula thus derived, $0.001 w^{0.63}$, expresses the surface area of rats in square meters when the weight (w) is given in grams. That—for rat metabolism only—is this year's result of a century of surface law!

Reducing the metabolic rate to a power function of body weight such as the $2/3$ or $3/4$ power is valuable and essential for some problems in comparative physiology. Every scientist also should, of course, be free to use any surface he likes, but the time is ripe for asking authors, who use their personal rat surfaces, to supplement their figures with data which make their results comparable to those of other workers: the metabolic rate per animal or per unit weight should be given together with the weight of the animal. Work in bioenergetics would benefit greatly if the editors of our journals, possibly backed by recommendations of the National Research Council, insisted on such standard supplement of the results on metabolic rates.—This is the second centenary wish.

AGE AND METABOLISM

Infants and children.—A slight tendency for the metabolic rate per unit surface of infants to rise with increasing age from 200 to 600 days was noted by Benjamin & Welch (10). For the later development of children, however, Lewis and co-workers (11), checking their earlier metabolic studies with a new series of 946 respiration trials on 102 children, found a consistent decrease of the metabolic rate per unit surface with increasing age from two to twelve years. This decreasing tendency of metabolic rate with increasing age was also observed by Lewis and co-workers (12) in experiments with thirteen- to fifteen-year-old youngsters.

The mean metabolic rates per unit surface of these children (in Denver) were consistently lower than the corresponding rates measured in four other laboratories, but they parallel those other results in the increase of the metabolic rate with increasing age (13).

Menarche.—Shock (14) measured the basal metabolic rate of fifty girls at six months' intervals over a six-year period starting at the age of eleven. He concluded that the beginning of menstruation marks a rapid decrease in the basal metabolic rate per unit of the DuBois surface. This period of rapid decline in the rate of oxygen consumption is more closely associated with the beginning of menstruation than with age in years. Along with the decrease in metabolic rate at the beginning of menstruation, blood pressure and pulse rate also changed to the adult level.

College women.—The basal metabolism of college women has been extensively investigated at the Agriculture Experiment stations of Iowa, Kansas, Minnesota, and Oklahoma (15). As the authors show, the insistence upon a certain check between two results, as a criterion for using or discarding the data, not only reduces the available information but also introduces into the variance a bias that may invalidate the statistical test for significance.

Some data on human metabolism are discussed in the section on the metabolic effect of changes in oxygen pressure.

Young rats.—Age from birth to sexual maturity apparently affects the metabolic rate per unit surface of rats and humans in just the opposite way. Kibler & Brody (16) carried out repeated respiration trials with four male and four female rats, from birth to four months of age. They found that the metabolic rate per square meter of body surface rose to a maximum at the age of forty-five days. A further increase in age to four months gradually decreased the daily metabolic rate. Brody (17) reports a higher metabolic rate for fast-growing rat babies of a small litter than for slower-growing ones of a large litter. The state of nutrition, which affects both growth rate and metabolic rate, probably should be considered.

The low metabolic rate in newly born rats may be correlated with the low frequency of heart beat at birth reported by Marcuse & Moore (18) after measurements with the electroencephalograph. The low metabolic rate also may be connected with a relatively

late development of the thyroid function. Gorbman & Evans (19) observed that in the rat the functional ability to store iodine begins in the eighteenth to nineteenth day of fetal life, thus almost at birth.

Age and metabolism of human placenta.—Wang & Hellman (20) concluded from microrespiration trials that the metabolic rate of human placenta *in vitro* decreases as pregnancy advances.

ENDOCRINES AND ENERGY METABOLISM

The most active field of research on energy metabolism at present is the relation of the endocrine system to the regulation of the metabolic rate.

Anterior pituitary extract (growth hormone).—Earlier measurements on fasting katabolism of rats as affected by prolonged injections of anterior pituitary extracts (21) have been repeated by Voris and co-workers (22, 23). The number of different conditions was considerably extended and the number of rats for one condition considerably decreased. The growth-promoting effect of the extract in the male rats seemed soon to be counteracted, and after eighty-eight daily injections the noninjected controls weighed more than the injected males. In the females, however, the pituitary extract promoted growth as in earlier trials. The injected rats pair-fed with the controls showed an increase of 18 per cent; the injected rats on unlimited food intake an increase of 36 per cent of the weight of the noninjected controls.

The authors conclude with a paradoxical statement: "The A.P.E. (anterior pituitary extract) appeared to act as a specific stimulant of cellular metabolism and, at the same time, was effective in promoting an increase in body substance which was less energetic than that assimilated normally." By "less energetic" the authors no doubt mean body substance with a lower metabolic rate. In spite of this result they speak of stimulation of cellular metabolism, apparently being misled by interpolation and extrapolation of the metabolic rate to a standard weight of 200 gm. In using the regression of metabolic rate on weight they neglected the correlation of age and weight in their rats, and therefore eliminating differences in size they introduced differences in age. Their injected rats had a higher metabolic rate at the weight of 200 gm., not because prolonged injections of growth hormone stimulate cellular metabolism, but because the injected rats reached the weight

of 200 gm. at an earlier age when the metabolic rate is higher. The heat production per gram of body weight is smaller for the injected than for the control rats. Voris' figures, contrary to his conclusions, confirm earlier results that prolonged injections of anterior pituitary extract have a decreasing rather than a stimulating effect on tissue metabolism. In the earlier trials this effect was noted even in the diaphragm *in vitro* (21).

A parallelism between changes in metabolic rates *in vivo* and *in vitro* was observed recently also by Raska (24) who noted a considerable decrease in the metabolic rate *in vitro* of ischemic as compared to normal kidneys of dogs and rabbits.

That anterior pituitary extract may have an immediate calorigenic effect (as distinguished from the chronic effect just discussed) is indicated by results of Archer and co-workers (25), who used four pairs of male rats for six-hour respiration trials, immediately following the last of three daily hormone injections (with one of each pair) at the end of each of four consecutive two-week series of paired feeding. The calorigenic effect of the hormone was independent of the previous feed (ordinary stock, high protein, high carbohydrate, and high fat diet). It was also the same after twenty-four hours of fast.

To appraise the data is somewhat difficult because the variability of the heat production (or of the differences between pair mates) is not given. Neither was the metabolic rate of the four injected rats compared with that of the controls before the injection or after the cessation of the effect. This would have been particularly important because the same rats seem to have served either as injected rats or as controls throughout the trial. The consistency of the effect is therefore no indicator for its significance, since different groups of rats may under apparently equal conditions have consistently different metabolic rates. The excess of the metabolic rate of the hormone rats, however, averages to 14 per cent of the metabolic rate of the controls—a difference that suggests a significant effect.

From comparison of (rather small) numbers of metabolism trials with growing chicks Nalbandov & Card (26) suggest that the decrease in metabolic rate following hypophysectomy may be the effect of a decrease in food intake.

Houssay (27) has written a review of twenty-five years of research on the role of the hypophysis in carbohydrate metabolism.

Antithyrotropic principle of the hypophysis.—Not only does hyperthyroidism produce an immediate counter action from the pituitary by decreasing the production of thyrotropic hormone, but the hypophysis that has been under the influence of hyperthyroidism maintains its acquired antagonism to the thyroid when it is transplanted from one animal to another. Thus Reforzo-Membrives (28) observed that injection of rat hypophysis into guinea pigs (whose thyroids seem particularly responsive to thyrotropic hormone) had opposite effect when the thyroid condition of the donor rats was changed. Hypophyses from normal rats injected into guinea pigs increased the weight of the guinea pig thyroid whose oxidation index (oxidase content measured by colorimetric tests with *p*-phenylene diamine) was increased 28 per cent above normal. Hypophyses from thyroid-fed rats, on the other hand, injected into guinea pigs decreased the weight of the guinea pig thyroid. The oxidation index of the thyroid tissue was lowered 23 per cent and the basal metabolic rate of the guinea pigs was decreased.

Drugs with negative calorogenic (antithyroid) action.—Earlier observations on goiterogenic effects of sulfa drugs (29, 30) have been confirmed by MacKenzie & MacKenzie (31). The research has been extended to older rats, guinea pigs, dogs, and chickens and has been supplemented with respiration trials on rats. In a two-week trial with young rats the relative thyroid weight appeared to be a linear function of the concentration of sulfaguanidine in the diet. The weight of the moist gland rose from 7 mg. per 100 gm. body weight without the drug to 38 mg. per 100 gm. body weight when 3 per cent sulfaguanidine was in the diet. The goiterogenic action of sulfaguanidine in mature and in old rats resembled that in young rats; but the older the rat, the longer the time required to produce a given effect.

The basal metabolic rate of fourteen adult rats with 200 gm. body weight was measured after a twenty-hour fast in weekly intervals for three weeks when eight rats were fed 2 per cent sulfaguanidine in the diet; and the respiration trials were repeated for a duration of forty days. A mean decrease of 10 per cent was observed at the end of the first week on the drug. After two weeks of feeding the drug, the metabolic rate was decreased 20 per cent; and it remained at that level for three weeks further.

Various dietary supplements, including fresh liver, failed to

prevent the goiterogenic action of sulfaguanidine. Sodium iodide, fed with 0.5 per cent sulfaguanidine in a purified diet, seemed to increase rather than decrease the goiterogenic effect. Desiccated thyroid or thyroxine, however, prevented the effect. The daily administration of 10 mg. of thyroxine per 10 gm. of body weight to rats receiving 2 per cent of sulfaguanidine, and with basal metabolic rates of 20 per cent below normal, brought about a rise in oxygen consumption within twenty-four hours, which resulted in basal rates of plus 20 per cent by the eighth day. The drug had no effect on thyroidectomized rats—at least not on those in which the completeness of thyroidectomy was indicated by a decreased basal metabolic rate. In two out of five thyroidectomized rats this rate remained at the normal level. In those rats sulfaguanidine decreased the metabolic rate. Thyroxine increased this rate of all rats to normal.

The sulfa drugs that had a goiterogenic effect also produced histological changes in the pituitary gland similar to the changes observed after thyroidectomy. The authors therefore conclude that sulfonamides and thioureas probably depress primarily the functional activity of the thyroid and hence the basal metabolic rate, and that the thyroid hyperplasia reflects an increased pituitary activity resulting from this depression.

The results of the MacKenzies are confirmed in a simultaneous publication by Astwood and co-workers (32) who conclude that "the mechanism of the goiterogenic action of the substances investigated resides in an interference with the synthesis of thyroid hormone." They give the following account of the probable sequence of events: the sulfa drug lowers the rate of synthesis of thyroid hormone; the lower concentration of thyroid hormone leads to an excess of thyrotropin (produced by the pituitary gland), which in turn stimulates thyroid gland hyperplasia (histologically detectable within forty-eight hours from first application of the sulfa drug). The thyroid gland releases its normal store of thyroid hormone, keeping the metabolic rate normal for a few days. In seven to ten days this compensatory supply of thyroid hormone to the blood stream becomes exhausted, and then the metabolic rate decreases. Astwood and co-workers, in addition to determinations like those of MacKenzie & MacKenzie, measured the effect of the sulfa drugs on food intake and growth rate. These two functions became significantly depressed about twenty-five

days after the addition of 2 per cent sulfaguanidine to a stock ration fed to three- or four-week-old rats. Hypothyroidism produced by hypophysectomy led to the same low food intake and growth rate as 2 per cent sulfaguanidine in the food.

A drug that inhibits the formation of thyroid hormone may lead to a more severe hypothyroidism than even thyroidectomy since the formation of diiodotyrosine and the conversion of inorganic iodine to thyroxine in rats, completely deprived of their thyroid glands for several months, has been established by Morton and co-workers (33) using radio active iodine. This extrathyroid production of thyroxine may possibly also be inhibited by sulfa drugs.

Assay of thyroid hormone.—Dempsey & Astwood (34) made use of the "anti-thyroid" drug thiouracil (preventing the formation of thyroid hormone by the thyroid gland) in order to assay the amount of thyroid hormone normally produced.

Thyroid hormone and injected thyroxine decrease the thyrotropic activity of the pituitary gland, which in turn influences the weight of the thyroid gland. This weight is used as a criterion for the level of thyroid hormone. Young male rats weighing 80 to 120 gm. were given thiouracil as 0.1 per cent solution in their drinking water. Their thyroids became enlarged (uninhibited effect of pituitary gland). This enlargement developed most rapidly at a low environmental temperature. It developed slowly when the rats were kept in an environment of 35°C., a fact indicating that the metabolic rate parallels the rate of depletion of thyroid hormone after its production has been inhibited by the sulfa drug.

When thyroxine was injected hypodermically in doses varying from 0 to 20 micrograms daily per rat, the relative thyroid weights after fourteen days decreased systematically. This result indicated that injection of sufficient thyroxine can completely inhibit the production of thyrotropic hormone. Higher doses of thyroxine do not further reduce the size of the thyroid gland. The dose of thyroxine which in a functionally dethyroidized rat produces the normal relative thyroid weight (7 to 8 mg. per 100 gm.) is considered the equivalent of the normal daily rate of production of thyroid hormone.

The results based on thyroid weights were checked by measurements of the basal metabolism. Feeding thiouracil lowered the metabolic rate 16 per cent in nine to twelve days and as much as

53 per cent in two to three months. Daily injections of 5 to 10 mg. thyroxine restored the metabolic level to normal.

Thyroidectomy.—Marvin & Smith (35) found that thyroidectomy depressed the basal metabolic rate of pigeons 27 per cent.

Adrenal cortex and metabolism.—The metabolic role of the adrenal gland, particularly the cortex, is still under study. Some of this research is discussed in the section on oxygen pressure (page 135). Reviews on the function of the adrenal cortex have been written recently by Hartman (36) and by Ingle (37).

Butcher (38) maintained young rats at a weight of 40 to 50 gm. by a daily ration of only 4 gm. of food. He adrenalectomized twelve rats and kept thirteen controls. Microrespiration trials with slices from the skin on the backs of the controls consumed *in vitro* 0.88 c.mm. oxygen per mg. dry per hr., whereas the skins of adrenalectomized rats had a Q_{O_2} of 1.00 c.mm. per mg. dry per hr. forty-six hours after adrenalectomy, and of 1.25 c.mm. per mg. dry per hr. sixty-six hours after adrenalectomy.

The reverse of this investigation (with the adrenal gland or cortical hormone level as the independent and the metabolic rate as the dependent variable) has been active—namely, research on the effect of metabolic processes on the adrenal gland.

Mulinos & Pomerantz (39) observed that complete starvation increased the weight of the adrenal gland of rats, whereas chronic underfeeding (6 gm. of diet per rat per day, or about one half the normal ration) decreased the absolute as well as the relative adrenal weight.

Tepperman and co-workers (40) relate this effect of total and partial starvation on the adrenal weight to metabolism. In total starvation the animal maintains a proper level of energy metabolism by a relatively intensified breakdown of body protein—increasing the concentration of a substance "S" (possibly a product of incomplete protein katabolism) in the body fluids. The katabolism of this extra amount of substance "S" inactivates, "uses up," an increased amount of cortical hormone, lowering the level of this hormone and thus decreasing its inhibitory action on the adrenotropic activity of the anterior lobe of the pituitary gland. The same authors (41) observed that a hypertrophy of the adrenal gland may also be produced by high-protein diets (substance "S" can originate from dietary protein) and demonstrated by enucleation that the hypertrophy was mainly a growth of the cortex. The

rate of oxygen consumption of the rats after twenty-four hours' fast was independent of the protein level in the previous diet.

Ingle and co-workers (42) could find no influence of the protein-to-carbohydrate ratio in the diet of rats on survival time after adrenalectomy, or on the weights of the adrenal glands. The difference in age of the rats may account for the discrepancy in the results between the two laboratories.

Epinephrine and metabolic rate.—Smith & Matthews (43) discovered a parallelism between metabolic and color effect of epinephrine in a marine fish, *Girella nigricans*. Doses of epinephrine that had no paling effect on the skin did not change the rate of oxygen consumption. Higher doses that produced a paling (by concentrating the melanophore pigment in spots) decreased the metabolic rate. The dark skin of the fish reappeared simultaneously with the return of the normal level of oxygen consumption, unless the dose was high enough to produce immediate paling, in which case the metabolic rate dropped continuously until the fish died.

In rats epinephrine injections, in contrast to the effect in fish, raise the metabolic level. Bunnell & Griffith (44) injected 0.02 mg. of epinephrine subcutaneously into male rats, ranging in age from two to twenty-eight months, and observed an average maximal increase of 34 per cent of the basal metabolic rate within forty-five minutes after the injection and a metabolic level still 5 per cent above basal four hours after the injection. The calorigenic effect as well as the return to normal is delayed in proportion to the age of the rats, a situation explained by the authors as the result of delayed absorption of the drug.

According to Bunnell & Griffith the increase in metabolic rate during the first hour after injection is partly due to the restlessness that epinephrine causes. They claim, however, that their results are probably not greatly affected by the overt muscular tremor characteristic of this initial period of action of the hormone. To exclude such effects, the authors confined the results of their measurements to those short intervals in which the animal was not actually moving about. The measurement of metabolic rates, and particularly respiratory quotients, in short selected periods between periods of activity appears somewhat dangerous: not only has the animal a lag between activity and the effect of this activity on the respiratory exchange during which it can develop oxygen

deficits and wash out carbon dioxide, but the respiration apparatus itself may have an additional lag, which may be different for oxygen and for carbon dioxide measurements.

Appetite and metabolism affected by endocrines.—The appetite of an animal probably is decidedly influenced by its energy requirement. Warkentin and co-workers (45) have confirmed this idea by selective feeding tests combined with respiration trials on normal rats of various ages, on rats fed desiccated thyroid, and on thyroidectomized rats. These authors observed that older rats eat less food per unit weight than do young rats, the critical age between old and young being four months. Considering the close relation between metabolic rate and food capacity, it would have been advantageous to express both functions in the same unit of body size, instead of giving the metabolic rate per unit of surface area and the food intake per 100 gm. of body weight. The rats fed thyroid ate much more per unit weight than the normal rats.

Samuels and co-workers (46) overcame the difficulties of decreased appetite in hypophysectomized rats by feeding them, through a stomach tube, rations that produced slight gains. The hypophysectomized rats stored less protein but more fat than the controls.¹ This example shows that a pathological condition may interfere with protein utilization without decreasing the efficiency of energy utilization.

Animals with a reduced metabolic rate as a rule lose appetite. When, however, their food intake is kept at a high enough level, and if their absorption and excretion are not sufficiently changed, they must deposit the excess food energy as body substance. Fat deposition may then be regarded as a reaction to compensate for a relative lack of katabolic capacity.

If an animal's food intake is not limited by its energy requirement—a genetically conditioned state of some yellow mice observed by Rytand (47)—obesity results.

Drill & Shaffer (48) observed in dogs that lack of vitamin B overcompensated the stimulus for increased food intake set by hyperthyroidism. Supply of vitamin B₁ restored the appetite,

¹ The metabolic rate calculated by Samuels and co-workers from energy balances (table 2, p. 91) seems to include the energy in urine. The metabolic rate in this table very likely is given per square decimeter not per square meter of body surface as indicated.

but only additional supply of the B₁ vitamins (yeast) enabled the thyroid fed dogs to maintain also their body weight.

Adrenalectomy of pigeons according to Miller & Riddle (49) decreased the food intake to one-fifth of normal. Daily injections of either adrenal cortex extract or prolactin partially restored the appetite. These effects appeared to be additive when both hormones were injected.

Those aspects of energy metabolism relating to temperature regulation will be found in the chapter in this volume on "Physiological Effects of Heat and Cold."

OXYGEN PRESSURE AND ENERGY METABOLISM

The various physiological aspects of anoxia are discussed thoroughly in Van Liere's book (50). Special problems are reviewed by Grant (51), Dill (52), and Graybiel (53).

Range of altitudes without metabolic effect.—Lewis and co-workers (54) measured the basal metabolic rate of two men and five women at Stillwater, Oklahoma (910 feet altitude), and at Denver, Colorado (5,280 feet altitude). They also measured the basal metabolic rate of one man and three women from the same group at El Dorado, Colorado (8,720 feet). The persons were adapted to each level by several weeks' residence; and this adaptation was checked by blood studies (55), which showed increasing number of red cells, hemoglobin, and packed cell volume with increasing altitude. Lewis and co-workers found no metabolic effect of change in altitude within the range studied.

This result was confirmed (56) by comparing the basal metabolic rate of forty-three women between the ages of seventeen and twenty-six, who had resided at Denver for at least a year, namely 31.8 kcal. per sq. m. (of the DuBois surface) per hr., with the averages of women near sea level secured by other workers—for example, Tilt & Walters (57), whose results averaged 31.7 kcal. per sq. m. per hr. There are undoubtedly statistically significant differences between the means of the basal metabolic rate measured by different workers at different localities, but these differences in the metabolic rates up to an altitude of 8,000 feet are not correlated to the altitude of the different locations. This conclusion was recently adopted also by McCrery and co-workers (58).

Maximum altitude.—From experiments with twenty-seven

young men breathing gas mixtures with oxygen content corresponding to an altitude of 18,000 to 28,000 feet, Keys and co-workers (59) concluded that the heart is not the limiting factor in tolerance to acute hypoxia. No heart dilation was observed at the dilutions of oxygen used. An increase of the partial oxygen pressure up to one atmosphere caused a slight decrease in cardiac work, but changed neither the size nor the efficiency of the heart.

Hailman (60) reports that rats can stand lower pressures than the theoretical minimum assumed by Armstrong (61) to be 87 mm. Hg. in pure oxygen. Hailman explains this result as an effect of hyperventilation, which reduces the tension of water vapor as well as carbon dioxide in the alveoli below the values of 47 and 40 mm. respectively (used by Armstrong for his deduction). Hailman demonstrated this effect by keeping nine rats for twenty minutes, at a pressure of 75 to 90 mm. which leads to hyperpnea, and observing that the respiratory failure of these rats occurred at an average of 60 mm. Ten other rats, which did not have the extra time of hyperventilation, failed at 65 mm. oxygen pressure. The difference is, however, statistically not quite significant.

Circulation anoxia.—Anoxia produced by hemorrhagic shock does not affect the metabolic ability of the tissues. Beecher & Craig (62) measured the *in vitro* rate of oxygen consumption of cerebral cortex, kidney cortex, heart muscle, and liver slices of fifty-seven cats. Shock was produced by bleeding until the blood pressure fell to below 70 mm. Hg and the rectal temperature decreased. There was no significant difference in the rate of oxygen consumption and the rate of lactic acid production *in vitro* between the tissues from shocked and those from normal cats. The authors conclude: "The drop in the total resting metabolic rate commonly found in shock is apparently not dependent upon abnormality in the peripheral cells."

Engel and co-workers (63) interpret changes in the composition of blood during hemorrhagic shock in rats as the result of a decrease in hepatic function following early anoxia in the liver, and later effects of anoxia on the peripheral tissues causing an increased rate of protein and glucose breakdown with accumulation of lactate and pyruvate in blood and tissues.

Milder changes of circulatory conditions do not necessarily affect the metabolic rate. Thus Starr & Jonas (64) noted in human beings that hyperkinemia (supernormal cardiac output) and hypo-

kinemia (always judged by comparison with a normal value taking account of body size) are correlated with changes in the basal metabolic rate only, when these circulatory deviations are combined with hyper- or hypothyroidism. Essential hyper- or hypokinemia (not connected with thyroid abnormalities) did not affect the rate of basal metabolism.

As a change in circulation may lead to anoxia, so in turn anoxia may lead to changes in circulation. Abramson and co-workers (65) concluded from plethysmograph measurements on twenty-five humans that anoxia resulting from inhalation of a 10 per cent oxygen 90 per cent nitrogen mixture produced a small but definite increase in the rate at which blood flowed through the forearm and leg. On the other hand, Ershler and co-workers (66), observing nineteen healthy young men, noted that progressive anoxia produced by rebreathing air (with absorption of carbon dioxide on soda lime) led in seven subjects, who fainted, to a sharp rise in venous pressure just before syncope, a fact suggesting failure of the right ventricle. The circulation time (right arm to tongue) was decreased. When the subjects were allowed to breathe room air, all symptoms promptly disappeared.

The application of anoxia as shock treatment for schizophrenia was tested by Horvath and co-workers (67), who noticed that inhalation of gas mixtures with less than 5 per cent oxygen made schizophrenic patients unconscious in three to twenty minutes. Gas mixtures containing more than 6 per cent oxygen produced unconsciousness only rarely. From their experience with mixtures of 4 per cent oxygen content, equivalent to an altitude of 31,000 feet, Horvath and co-workers concluded that a jump from this altitude with an open parachute, reaching the level of 25,000 feet in about three minutes, should have no permanent ill effects from anoxia of the central nervous system, even without oxygen equipment.

Effect of drugs in acute anoxic anoxia.—For immediate fatal effects of anoxia, the air pressure has to be much lower than for chronic effects. Above an altitude of 11,000 meters (36,000 feet) with the air pressure dropping below 170 mm., even breathing pure oxygen does not prevent acute anoxia in man (52).

Emerson and co-workers (68) noted that 50 per cent of mice in air at pressures below this limit die within a few minutes. Full narcotic doses of ethyl alcohol (6 cc. per kg. body weight) reduce

the lethal effect of acute anoxia significantly if the drug is given only one hour before the exposure to low oxygen pressure. The protective effect of alcohol is lost fourteen hours after administration. Emerson & Van Liere (69) have worked out a method for measuring the tolerance to low pressure. Mice treated with a drug and control mice are placed in low pressure tanks at the same time. The pressure is rapidly decreased, simulating an ascent to 10,000 feet altitude. The mice remain at this pressure for 10 minutes, which suffices to prevent aeroembolism later; then the "ascent" is resumed at a rate of 1,000 feet per minute until about 50 per cent of the control mice are dead. The tolerance of the treated mice is assayed by their mortality ratio compared with that of the controls. Some drugs such as ephedrine hydrochloride (25 mg. per kg.) increased the lethal effect of low air pressure; others such as epinephrine hydrochloride (0.3 mg. per kg.) had no effect; and others acted prophylactically like ethyl alcohol—for example, ergotamine tartrate (5 mg. per kg.) and physostigmine salicylate (1 mg. per kg.) (70).

Chronic anoxia and adrenal cortex.—Sundstroem & Michaels (71) conclude, from their extensive work with rats kept in low pressure tanks, that the high altitude syndrome results mainly from a corticoadrenal insufficiency. They subscribe to the old recommendation of Thomas (72) that adrenal preparations be used against mountain sickness. These authors base their theory on the following: (a) syndromes of corticoadrenal insufficiency and low pressure disease are similar; (b) adrenalectomized rats suffer more (die sooner) from decrease in air pressure than do normal rats; (c) death of adrenalectomized rats can be postponed by charcoal preparations of adrenal cortex in doses which must increase progressively as the air pressure decreases; (d) adrenal preparations on charcoal in the food help rats to survive on the average for two months at 260 to 300 mm. pressure, whereas the survival time of rats without this drug at the same pressure amounts to an average of one month only; (e) charcoal preparations of adrenal cortex in the food help the rats at low pressure to maintain their appetite; (f) rats with charcoal preparations of adrenal cortex in their food can endure strenuous exercise better than rats without the drugs (this was true for exercise under low pressure as well as for exercise immediately after the return from low to normal pressure); (g) rats adapted to low pressure contained

a surplus (compared with normal pressure rats) of a substance that resembled the cortical hormone in its ability to maintain adrenalectomized rats alive.

The critical pressure for rats appears to be 360 mm., corresponding to an altitude of 6,000 m. (20,000 feet). Above this level of pressure (below this altitude) mortality is practically independent of air pressure. A decrease in pressure below 360 mm., however, increases mortality. At 300 mm. (7,600 m. or 25,000 feet altitude) the number of deaths is an almost linear function of time: 25 per cent of the original number of rats die per week.

The basal metabolic rate at low pressure first increases (hyperfunction of adrenal cortex), then decreases below normal (exhaustion of adrenal cortex). Sundstroem & Michaels measured the metabolic rate of the low pressure rats at normal pressure, assuming, in line with Pflüger's law, that oxygen tension in blood or even in tissues could not act as a metabolic regulator. Since, however, Pflüger's law loses its application when the oxygen tension in tissues reaches zero, according to Krogh (73) and Thunberg (74), the validity of this argument seems questionable especially for conditions of oxygen deficiency. Sundstroem & Michaels themselves write that "the curtailment of blood is known to reduce the use of oxygen to economical levels." Probably the metabolic rate of the rats just returned to normal from low pressure is still affected by the previous condition. Rapid changes in metabolic rate are possible, however, and the metabolic rate of low pressure rats should be measured at low pressure, since the metabolic after-effect of low pressure may differ from the effect itself.

The rate of oxygen consumption *in vitro* of liver slices from low pressure rats tends to decrease if the rats have been exposed to low pressure for two days only (adrenal cortex not yet adapted); to increase above normal for rats exposed for fourteen days to low pressure (adaptative hyperactivity of adrenal cortex); and to decrease again for rats exposed for twenty-eight days to low pressure (exhaustion of adrenal adaptation).

Thorn and co-workers (75), investigating the effect of repeated daily exposures to reduced oxygen pressures, particularly in relation to the adrenal cortex, concluded that adrenalectomized male rats cannot withstand repeated exposure to low barometric pressures unless treated with adrenal cortical hormone. They

noticed that exposures of young male rabbits to "high altitude" produced an increase in adrenal weight and that adrenalectomized dogs maintained on desoxycorticosteroneacetate did not tolerate repeated exposures to barometric pressures equivalent to altitudes of 25,000 feet. These investigators thus essentially agree with Sundstroem & Michaels.

NUTRITION AND ENERGY METABOLISM

On the role of vitamins and minerals in energy metabolism Potter (76) gives an illuminating glimpse of results obtained by research in enzyme chemistry. He compares life to an enzyme community in which inorganic phosphate and phosphate esters represent the medium of exchange of an essential evaluated in terms of energy, and adenine triphosphate is the pocket money.

Vitamin A deficiency.—Vitamin-A deficiency, according to Patterson and co-workers (77) produced a significantly lower body weight in rats compared with pair-fed controls supplied with vitamin A. The deficiency seemed to inhibit particularly the storage of body fat, thus affecting mainly energy utilization for fattening.

Vitamin B deficiency.—Williams and his co-workers (78) have shown that forty thyrotoxic patients with a basal metabolic rate at least 20 per cent above the normal had a decreased sugar tolerance, a higher content of pyruvic acid, and a decreased content of thiamine in their blood. They waste more thiamine not only by their higher metabolism but also by a greater excretion in the urine.

The basal metabolic rate in relation to vitamin B₂ deficiency was measured by Orsini and co-workers (79) with sixteen groups of two to seven, in most cases three rats per group. Riboflavin and pantothenic acid deficiencies did not affect the basal metabolic rate, but pyridoxine deficiency lowered it if expressed per unit of body surface. The variability of the results is not reported. The body weight of the deficient rats used in these trials amounts to only about one third to one half of that of the controls. The respiratory quotient of the deficient rats was higher than that of the controls; but the latter is itself above 0.8—a value not ordinarily found in rats that have fasted a day, which raises the question of the trustworthiness of the technique.

According to Voris & Moore (80) deficiency in vitamins of the B complex affected particularly the deposition of body fat much as did the lack of vitamin A reported above. The deficiency of thiamine, riboflavin, pyridoxine, and pantothenate respectively, in groups of five pairs of male and five pairs of female rats, was mild enough to allow considerable growth without significant differences in the increases of body protein between the deficient and the pair-fed control rats. In some cases, especially in riboflavin deficiency, the deficient rats stored less body fat than the controls. The difference between the group averages of deficient and control rats, however, as judged from the data given, are in no instance statistically significant.

The sexual cycle, activity, and survival time of rats kept on glucose *ad libitum* with or without thiamine has been observed by Richter & Rice (81). The rats receiving thiamine exhibited signs of vitamin A deficiency, and the thiamine-deficient rats were in a constant state of diestrus. The activity (measured in a rotating cage) was maintained for twenty days when glucose and water were available, and for fifty days when the rats had access to thiamine. The survival time for rats on water alone was four days; on glucose and water thirty-seven days; and on glucose, thiamine, and water seventy-four days. The survival time seems closely correlated to the intake of food energy (glucose in this case), which in turn is governed by the intake of thiamine.

The calorogenic effect of carbohydrate and fat as affected by thiamine was measured by Ring (82) in three series of three trials each, conducted at weekly intervals with eight rats. After the measurement of the basal metabolic rate the rats were given by stomach tube 3 cc. of 50 per cent glucose; then the respiration trial was continued for seven hours. A week later the procedure was repeated with the addition of 50 μ g. of thiamine. Two weeks later 1.5 cc. oleic acid was added. Thiamine alone without glucose raised the basal metabolic rate 0.9 per cent; glucose alone 4.2 ± 0.4 per cent; glucose plus thiamine 8.0 ± 0.5 per cent; and glucose plus thiamine plus oleic acid 6.7 ± 1.0 per cent of the basal rate. The author's explanation that thiamine raises the calorogenic effect of glucose because it facilitates the deposition of body fat is paradoxical. It would seem simpler to assume that, on the contrary, thiamine favors the oxidation of glucose rather than its conversion to body fat, and that the lower calorogenic action

without thiamine results from a limited rate of glucose combustion.

Vitamin E deficiency.—Houchin & Mattill (83) measured the *in vitro* oxygen consumption as well as the creatine and chloride content of muscles from fifty-nine normal and vitamin-E-deficient dystrophic rabbits, rats, and hamsters. Dystrophic muscles from vitamin-E-deficient animals had an increased oxidation rate *in vitro*. This rate for muscles from vitamin-E-deficient hamsters was as high as 250 per cent of the rate of normal hamster muscles. The metabolic rate *in vitro* appeared to increase with increasing severity of the dystrophic condition. Muscle material obtained from rabbits by biopsy was used for Warburg trials, which indicated that α -tocopherol acetate, given by mouth, lowered the originally high metabolic rate *in vitro* of muscles from vitamin-E-deficient rabbits to the normal low level in ten hours.

Tocopherol added to the muscle *in vitro* lowered its rate of oxygen consumption. Houchin (84) concludes that α -tocopherol "in the form of its phosphate acts as a brake on the oxidative mechanism, primarily of skeletal muscle, and in its absence these oxidative processes run riot. An altered creatine metabolism is one of the results of this disturbance."

Kaunitz & Pappenheimer (85) confirmed the lowering effect of tocopherol on the tissue metabolism. The pectoralis muscle of chicks on vitamin-E-deficient diet consumed *in vitro* an average of 6.1 ± 0.22 c.mm. per mg. dry per hr. One dose of tocopherol lowered the Q_{O_2} *in vitro* to 5.3 ± 0.23 . The Q_{O_2} of rat muscle, according to Kaunitz & Pappenheimer's data, appears to be the same for rats on the stock diet and for vitamin-E-deficient rats; but tocopherol, added to the vitamin-E-deficient diet, lowered the metabolic rate *in vitro*. The decrease of *in vitro* oxygen consumption when tocopherol was added to a vitamin-E-deficient diet could be observed before muscle dystrophy was evident. The metabolic rate of rats on a stock diet was similar to that of rats on a vitamin-E-deficient diet.

Mineral deficiencies.—Cohn & Soskin (86) observed that dogs depleted of sodium chloride had an abnormally low metabolic rate, which these workers restored to a normal level by providing sodium chloride. Injection of this salt in normal dogs increased the rate of oxygen consumption. This result at first sight seems to

contradict the observations of Kriss & Smith (87) that a low-salt diet led to an increase in metabolic rate of rats compared with that of normal controls. The contradiction is not necessarily real, however, since there may be a difference between metabolic reaction to acute disturbances of the mineral balance and the effects of chronic mineral deficiencies. Cohn & Soskin's experiments were, furthermore, carried out with changes particularly of the chloride balance, whereas the deficiency of "inorganic salts" in the earlier work involved several components, particularly important kations.

A slight and erratic tendency toward a lower basal metabolic rate of iodine-deficient rats has been reported by Remington and co-workers (88).

Potassium deficiency, according to Follis (89), produced more severe lesions in the myocardium of rats that had been exercised than in that of nonexercised rats.

WORK

Tissue glycogen.—An excellent review on the significance of tissue glycogen has been written by Soskin (90). The level of tissue glycogen, an important criterion of an animal's fitness for prolonged work, is compared to the level of water in a storage tank supplied from a well (blood sugar) by a pump (phosphorylation of sugar). The tank (muscle glycogen) in an emergency yields a stream at the tap (work) exceeding the capacity of the pump.

Fitness for different work.—The criteria of endurance for different types of work have been analyzed by Dill (91). For stress of short duration (sprinting) the work is done anaerobically, leaving a high level of blood sugar (150 to 200 mg. per cent) and lactic acid (150 mg. per cent) in the blood stream at the end. For effort of long duration (a Marathon race) on the contrary, the organism must keep nearly normal conditions by aerobic processes during work. The level of sugar and lactic acid in the blood stream at the end of the stress should not exceed 50 to 60 and 15 to 20 per cent respectively.

Ischemia.—The metabolic effects of local interruption of blood circulation (ischemia) were measured by Barman and co-workers (92). The ischemia of 1 to 1.5 min. duration was produced by sphygmomanometer cuffs around the legs of men walking on a

treadmill. Shutting off the circulation of the legs reduced the ventilation rate as well as the rate of oxygen consumption of a man 25 per cent. Relief of the ischemia increased the rates of ventilation and of oxygen consumption as well as the level of blood lactate far above normal values. The return to normal conditions was speeded up when the subject continued to walk. The rate of repaying the oxygen debt and the rate of removal of lactate, which diffuses rapidly from the muscles to the venous blood, were not in a simple relation. The changes in the rates of oxygen consumption and that of cardiac output during the recovery period after exercise according to Barman and co-workers (93) are nearly equal. The rate of ventilation decreases more slowly, and the removal of excess lactate from the blood stream is the slowest of the recovery processes. The ventilatory efficiency (rate of oxygen consumption per unit of pulmonary ventilation) is smaller after exhausting work than after moderate exercise.

Nutrients.—The relation of nutrients and drugs to work performance has been investigated by several laboratories. Wrightington (94) reports that the partial efficiency of work (heat equivalent of work per unit of increase in metabolism during work and recovery) measured in ten-minute work periods, of male students on a bicycle ergometer, was about 20 per cent and was not affected by feeding glucose or sucrose.

Ketone bodies can be utilized by muscles during work, according to Neufeld & Ross (95), who report, however, that this utilization becomes apparent only during deficiency of carbohydrate stores.

Vitamins.—A vitamin-A-deficient diet ingested by men for 3 to 4½ months did not affect their plasma vitamin-A level, their visual threshold, or their fitness for moderate or exhausting work, according to Wald and co-workers (96).

The influence of B-complex vitamins on the fitness of men for work was studied by Johnson and co-workers (97) on ten healthy men who were served a basic diet that was low in vitamins of the B complex. Thiamine (2 mg. per day), whole brewers' yeast, or placebos was added to the diet. The caloric intake was unlimited; and the choice of foods, within a given limit, was free. The subjects performed work by pulling a stoneboat over a flat course of three hundred yards with a force of one third their body weight and a rate of one yard per sec. The "fitness index"

(duration of standard work per sum of pulse rate at given intervals of recovery) decreased during a week on the basic diet, and there were subjective symptoms, such as poor appetite. These symptoms were less severe when thiamine was given, but even with thiamine the fitness index decreased during the first week, whereas during the second week with yeast it increased again and all subjective symptoms of deficiency disappeared. Unfortunately all subjects received yeast during the second week, so that there is no "no-yeast" control to check variables other than yeast, which possibly might have influenced the fitness index in the second week of the trial.

Netzley (98) described the use of a different test, though based on a similar principle—performance of standard work with regard to body weight—and using changes in pulse rate and blood pressure as criteria of tolerance. He used this test to measure chronic fatigue in children.

The work output of four trained students as a function of mild vitamin-B deficiency was measured by Barborka and co-workers (99). The students were trained to the work on an electrodynamic brake ergometer for nine months while receiving a well-balanced diet with sufficient vitamin content. For a period of two months they received a diet mildly deficient in vitamin-B complex, such as many ordinary Americans consume without exhibiting symptoms of vitamin deficiency. A three-week period followed in which carbohydrates were increased and fat was decreased. The trial was then concluded by a four-week period with the students on the second diet, but supplied with a yeast concentrate in tomato and lemon-juice mix. The changes in the vitamin intake were clearly indicated by the urinary level of thiamine and riboflavin. Irritability and other subjective symptoms were noted during the mild deficiency and promptly disappeared when yeast concentrate was added to the diet. A definite decrease of work output (work to fatigue in two consecutive periods separated by a ten-minute rest period) was observed during the deficiency periods, and an increase resulting from the added yeast concentrate. The variability of these results, necessary to judge the significance of the changes, is not reported.

Drugs.—Measuring the effect of drugs on performance and recovery of trained students doing rapidly exhausting work on a bicycle ergometer, Foltz and co-workers (100) noted that am-

phetamine increased neither work output nor speed of recovery; pervitine increased work output but did not affect recovery; and caffeine increased work output as well as speed of recovery.

Standing versus lying.—In repeated respiration trials with two horses Winchester (101) found no significant differences in the rate of oxygen consumption between trials in which they were standing and those in which they were lying.

Anaerobic work.—The armadillo (*Dasypus novemcinctus*), with a body temperature of only 33 to 35°C. and a metabolic rate of less than half that of normal homeotherms of equal size (2 to 3 kg. body weight), can burrow itself into the ground in a few minutes, thus performing considerable work while its respiration is impaired by dust. Scholander and co-workers (102) found the explanation for this apparent paradox. They noted in experiments with arrested breathing (by choking) that the armadillo, like some diving animals, is able to contract a considerable oxygen debt during its work. The armadillo would thus be a model for the sprinter mentioned above.

ENERGY METABOLISM OF ORGANS, TISSUES, AND SINGLE CELLS

This section deals only with metabolic research which has not been discussed already in the previous sections.

Brain metabolism.—The differences in sugar and lactic acid content of blood entering and leaving the brain of paretic patients indicate, according to Looney & Borkovic (103), that diathermy—used therapeutically—did not increase the metabolic rate of the brain.

Harreveld and co-workers (104), calculating the metabolic rate of brains of dogs *in situ* from arterial-venous differences in oxygen concentration and thermostromuhr measurements of blood flow, concluded that electronarcosis also does not affect brain metabolism significantly.

Elliot and co-workers (105) have observed, in Warburg trials with brain suspensions, that brain tissue oxidizes noncarbohydrate substances in the absence of an added substrate. When glucose is available (optimum concentration 10 mg. per cent), its oxidation accounts for almost the entire oxygen consumption. Pyruvate is katabolized as readily as glucose. Added lactate, however, is used up, like glucose and pyruvate, only by brain suspensions from insulinized animals.

Fuhrman & Field measured the relation between concentration of drugs and the metabolic rate of rat brain tissue *in vitro*. The inhibiting action of diphenyloxazolidinedione decreased with decreasing temperature (106). The concentration of some barbiturates necessary to produce 50 per cent inhibition of metabolic rate decreased with increasing length of the alkyl side chain (107). Glycolysis and oxygen consumption could not be separated by adding iodoacetate to the medium (108).

Mammary gland metabolism.—Powell & Shaw (109) noted a significant decrease in the concentration of lactic acid in blood entering compared with blood leaving the udders of seventeen cows. This decrease was correlated with a change in the hemoglobin concentration indicating excitement of the cows. In seventeen other cows in which the operation did not produce a change in hemoglobin content, there was also no significant change in lactic acid concentration. Powell & Shaw conclude that lactic acid is not utilized normally by the mammary gland.

Kleiber and co-workers (110) report a positive correlation between lactation activity and rate of oxygen consumption *in vitro* of the mammary gland of the rat, if this rate is expressed per unit dry weight (ordinary Q_{O_2}). If the rate is expressed per unit moist weight, however, there is no influence of lactation activity, and the respiration rate per unit weight of nitrogen is significantly lower for the lactating gland than for the inactive gland.

Structure and tissue metabolism.—Harreveld & Tyler (111) report that mincing nerve tissue reduces the metabolic rate of an optic nerve *in vitro* to a fraction of that obtained with a nerve sliced lengthwise, while the latter does not differ significantly from the rate of an intact nerve *in vitro*.

Electric energy.—Nachmansohn and co-workers (112) calculate from experiments with the electric eel that the breakdown of phosphocreatine is adequate to account for the electric energy released by this fish.

An electric power of 22 microwatts per sq. cm. of the wall of a dog's stomach has been measured by Rehm (113) and found to be of the same order of magnitude as the chemical work per unit of time corresponding to the normal rate of production of gastric juice. This work is equivalent to less than 4 per cent of the metabolic rate of the stomach wall.

Hair growth and skin metabolism.—The *in vitro* metabolism of rat skin, according to Butcher (114), shows a cyclic rate between

0.92 c.mm. oxygen per mg. dry per hr. and 1.31 c.mm. per mg. dry per hr. which parallels the cycle of hair growth. The peak of metabolic rate just precedes the increase in growth activity of the hair bud.

Spermatozoa metabolism.—A metabolic behavior unique for mammalian tissue—namely, the absence of the Pasteur effect—was observed on human spermatozoa by MacLeod (115). He measured the rate of oxygen consumption and lactic acid production, using the Warburg technique at 38°C. Glucose, succinate, pyruvate, fumarate, or lactate was added to glucose-free Ringer-phosphate solution for the various trials, so that the concentration of each of those substrates was 0.01 *M*. Reduction of methylene blue was used as a measurement for dehydrogenase activity. Even though the spermatozoa possess a cytochrome system (indicated by their ability to oxidize *p*-phenylenediamine), they cannot oxidize glucose or its anaerobic breakdown products, lactate and pyruvate. The spermatozoa produced as much lactic acid in an atmosphere of oxygen as they did in one of nitrogen. They oxidized succinate, but their motility with succinate as substrate failed as rapidly as without substrate, a fact from which MacLeod concludes that spermatozoa cannot utilize the energy from oxidation of succinate for mechanical work. The spermatozoa derive the energy for work solely from the breakdown of glucose to lactic acid. They retain their maximal motility in an atmosphere of nitrogen at 38°C. for many hours, but lose the motility rapidly when exposed to oxygen. The adverse effect of oxygen on human spermatozoa can, according to MacLeod, be explained by the formation of hydrogen peroxide, because addition of hemoglobin or catalase prevents the loss of motility in oxygen, and the addition of peroxide on the other hand (in amounts corresponding to that produced by the cells in oxygen, according to MacLeod's hypothesis) destroys the motility. Oxygen seems thus to be poisonous to spermatozoa, because they do not possess catalase, which protects other animal cells from possibly formed hydrogen peroxide.

An oxidation rate *in vitro* considerably higher than that observed by MacLeod with human spermatozoa was reported for spermatozoa of other species by Lardy & Phillips (116). These workers studied the effect of changes in mineral content of the medium on the metabolic rate.

Glycolysis and motility of bull sperm in the presence of glucose

were greatly depressed by lack of phosphate in the medium, but the rate of oxygen uptake was not considerably affected by changes in the phosphate content.

Microorganism metabolism.—The value of the energy concept is particularly obvious when the metabolic behavior of microorganisms is compared with that of animals: in the great variety of processes involved, the energy requirement for life remains the unifying principle, since all life is transfer of energy. The research in microbiology has revealed an amazing variety of ways and means by which microorganisms can derive this energy. Work on this subject has been reviewed this year by Van Niel (117).

For the autotrophic bacterium, *Thiobacillus thiooxidans*, Vogler *et al.* (118, 119, 120) discovered that the oxidation of sulfur is coupled to the transfer of phosphate from the medium to the cells. Thus even in the realm of some autotrophic microorganisms phosphate is used as the "means of exchange" of energy.

Cook & Kieke (121), measuring the poisonous effect of phenylmercuric nitrate on yeast by a reduction in the rate of oxygen consumption, confirmed earlier results that addition of yeast extract increases the metabolic rate of normal yeast.

Exploring the antimalarial effect of quinine, Wendel (122) measured the rate of oxygen consumption of defibrinated or heparinized blood from monkeys infected with malaria and found that nonnucleated blood cells, which normally have but a very low metabolism, consume oxygen at a considerable rate when they contain malarial parasites. At comparable acidities, lactate and glucose are equally good substrates for the respiratory exchange of the plasmodium, whose metabolism depletes blood of glucose within one-half to one hour but continues in the sugar-free medium for many hours. Addition of glucose as well as phosphate to the blood depresses the rate of oxygen uptake by the parasite.

That metabolism and growth can be maintained by marine bacteria at the cost of organic matter even when this is in extremely low concentration has been observed by Zobell & Grant (123) measuring the oxygen consumption of their cultures in sea water (whose content of organic matter had been reduced to 0.02 mg. per liter) by successive inoculations, sterilizations, and reinoculations. They added from 0.1 mg. to 100 mg. peptone per liter (in some trials glucose) and 1 mg. ammonium phosphate to the medium and noted that the rate of multiplication and that of

oxygen consumption in media with less than 10 mg. of organic matter per liter are directly proportional to the concentration of the substrate. Glucose, glycerol, ethanol, lactate, succinate, starch, and asparagine in concentrations ranging from 0.25 to 5 mg. per liter were quantitatively utilized by the bacteria in sixteen to thirty days at 20°C. From 60 to 70 per cent of the substrate was oxidized and 30 to 40 per cent was converted into bacterial protoplasm.

An even higher efficiency in the utilization of organic matter was observed by Doudoroff and co-workers (124), who report that underfed *Pseudomonas saccharophila* is able to convert two-thirds of the sucrose in the medium to cell material. Normally-fed bacteria (in 0.3 per cent sucrose solution) transfer 50 per cent of the sucrose to body substance. Undernutrition in this case seems to increase the total efficiency of food utilization of bacteria, whereas it decreases that of domestic animals. (In physiological papers "utilization" is often used confusingly. The term is understood here from the point of view of man, who spends food—in this case sugar—in order to get body substance of the organism.)

Fawns (125), reviewing the food production by microorganisms, reports yields of 25 kg. or more of dried yeast from 50 kg. of wood sugar. According to these results, microorganisms may be twice as efficient utilizers of food energy as our best domestic animals are and the rate of increase of microbiological food production is probably much less limited than the rate of a corresponding increase in the production of human food by domestic animals.

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RESPIRATION

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In preparing this review the main effort has been directed toward appraising the current status of certain fundamental questions in relation to respiratory control. In some instances it has proved impossible or at least undesirable to confine the discussion to papers which have appeared during a set interval of time.

THE ANATOMICAL AND FUNCTIONAL ORGANIZATION OF THE RESPIRATORY CENTER

It is probably safe to say that there is agreement currently among investigators that the primary neurones of the inspiratory and expiratory divisions of the vertebrate respiratory center are included in the reticular formation of the medulla and, further, that within the reticular formation they are confined within fairly well defined limits [see Gesell (1) for references]. Beyond this there are many aspects of the organization of the respiratory center concerning which viewpoints differ at the present moment.

The anatomical localization of inspiratory and expiratory centers.—Pitts, Magoun & Ranson (2), in their original paper on this subject, presented experimental findings which led them to believe that the inspiratory and expiratory neurones were segregated in two discrete regions, the former lying ventral to the latter in the reticular formation. This was contrary to the findings of Gesell, Bricker & Magee (3) and, later, of Brookhart (4), which indicated diffuse intermixing of the two types of neurones within the same region. In response to expressed doubts (1, 4) concerning the meaning of their findings, Pitts and coworkers have vigorously defended their original conclusions in a series of papers (5, 6, 7). The question is of sufficient importance to warrant critical examination of the additional evidence presented in order to evaluate its present status.

It will be recalled that the conclusions of Pitts *et al.* are based upon the finding (in cats and monkeys) that electrical stimulation of the medulla through bipolar electrodes (8 volts; frequency, 240 per sec.) caused maximal sustained inspiration when the electrode

tips lay in the ventral portion of the medullary reticular formation and maximal sustained expiration when the electrode tips lay in the dorsal regions. In order to test the reliability of this technique for locating structural entities within the central nervous system, Pitts (7) applied it to the differentiation of the bulbar trigeminal tract. Localization by this method agreed with known anatomical limits within 0.5 mm. The efficacy of the technique for localizing a relatively homogeneous nervous structure was therefore conclusively established. Nevertheless, the question which remains is whether the technique is capable of making the decision demanded in the present instance. It is well to recall that the alternative to segregation is intermixing of inspiratory and expiratory neurones and it is choice between these two alternatives rather than the spatial delimitation of a homogeneous structure which is at stake. The well established special functional interrelationship of inspiratory and expiratory neurones, namely the reciprocal inhibition of the other which accompanies activity of either type of cell, injects a crucial complication into the evaluation of stimulation studies as applied to the respiratory center. The inevitable result of application of an effective stimulus to a region containing both of these types of cell would be activity of one type alone with inhibition of the activity of the other—a result, indeed, which has been well demonstrated by Pitts (7, 8). Thus the stimulation technique could produce identical end results, especially when supramaximal stimulus strengths were used, regardless of whether it were applied to a region containing a mixture of the two types of neurones (with one type dominating because of superiority of numbers or of excitatory afferent connections) or to a region containing only one type alone.

The fact that there is no means of knowing the extent to which afferents to the respiratory neurones were involved in the results of Pitts *et al.* should invite caution in their interpretation. Intracranial section of afferent roots as practiced by Magoun & Beaton (6) is not a completely satisfactory control of this potential source of confusion since secondary or higher order afferent neurones and fibers would not be affected by such section. It may be pertinent to note that the frequency of stimulation used by Pitts *et al.* (240 per sec.) lies within the range which has been shown by Wyss (9) and by Rice (10) to cause dominance of expiration when applied to the central end of the cut vagus. On the other hand, when low frequency stimulation was applied to the dorsal medulla in the experiments of Pitts *et al.* (2, Fig. 5D) the reaction was no longer purely

expiratory but showed remarkable similarity to the results of low frequency stimulation as applied to the vagus (9, Fig. 2a *et seq.*). Furthermore, the figures of Monnier (11), who apparently used the technique of Pitts *et al.* except that high voltage, low frequency (30 per sec.) stimulation was used, fail to reveal any clear cut correlation between inspiratory and expiratory reactions and dorso-ventral position of the stimulating electrodes in the medulla.

All of this is not meant to imply that segregation of inspiratory and expiratory neurones in the reticular formation may not be the basis for the results of Pitts and coworkers. What is intended is to show that the reactions may be explained equally logically upon other bases and that the technique, valuable as it is for eliciting mutually exclusive inspiratory and expiratory responses, does not provide proof of the anatomical segregation of primary inspiratory and expiratory neurones.

Interpretation of the recently reported findings of Wyss & Croisier (12) may depend upon the ultimate answer to this question. Following destruction (by thermocoagulation) of the dorsal portions of the medial and lateral reticular formations of one side of the medulla, the "inspiratory effect" of low frequency stimulation of the vagus trunk was completely absent, while the "expiratory effect" (high frequency stimulation of the vagus trunk) remained unimpaired. The authors interpreted the result to indicate a localization of the inspiratory center dorsal to the expiratory center in the medulla, i.e., in exactly the reverse relationship to that postulated by Pitts, Magoun & Ranson. So far as the writer is aware, there is no support for this interpretation in numerous other studies of this question and it would seem that the results might be more simply explained upon the basis of a segregation of functionally similar intrabulbar vagus afferent pathways in such a way that the lesions inflicted could destroy all of one type while leaving others wholly or partly intact.

The ingenious experiments of Comroe (13) may also bear upon this problem. Using a fine hollow needle as a stimulating electrode and also as a means of injecting small amounts of chemical solutions at the site of the stimulating electrode, Comroe explored the brain stems of cats, comparing the responses to the two methods of excitation. Whereas the electrical stimulations (270 per sec.) usually produced inspiratory or expiratory apneas or a shifting of respiration toward inspiratory or expiratory levels, thus duplicating the results of Pitts, Magoun & Ranson, carbon dioxide-bicar-

bonate buffer solutions produced this result only rarely and, instead, usually caused a smoothly coordinated hyperpnea which involved the amplitude of both inspiration and expiration. A possible (and, to this writer, probable) explanation of this interesting result is significant in relation to the present question. Though there is no way of knowing whether the electrical stimulus was capable of exciting the cell bodies of the respiratory neurones directly, there is little reason for doubting its ability to activate both dendrites and axones. The chemical stimulus, on the other hand, would be expected to act directly upon or at the cell bodies, while it is highly questionable whether it would initiate impulses by direct action upon either dendrites or axons. The responses to electrical stimulation may then represent the results of afferent or efferent pathway stimulation, in accordance with the alternative interpretation of the results of Pitts, Magoun & Ranson suggested above, while the responses to chemical stimuli may represent the results of cell body stimulation, in which case they would suggest intermixing rather than segregation of inspiratory and expiratory neurones, since both inspiration and expiration were increased. If this method does provide a much needed means of distinguishing between fiber pathway and cell body responses, its systematic use may make possible the more precise localization of inspiratory and expiratory neurones, especially if minimal effective (and hence maximally localized) application of chemical stimulus is employed.

It would seem that none of the studies so far available have succeeded in proving either intermixing or segregation of inspiratory and expiratory neurones, nor does it seem probable that either alternative will be proven until methods are devised for distinguishing between cell body and fiber pathway responses. Meanwhile, the significance of the various recent studies would seem to lie in the points on which all agree, namely, that primary inspiratory and expiratory neurones are located in the medulla, that they are scattered diffusely in the reticular formations, and that they are confined within definite regions of the latter.

Automaticity in the central controlling mechanism.—Two aspects of the activity of the respiratory center are to be considered in this connection. These are the repetitive firing of the individual neurones and the rhythmic waxing and waning of the frequency of that firing associated with repetition of the respiratory act. Theoretically each might be either a purely reflex phenomenon or an inher-

ent (automatic) property of the cells of the respiratory center, and absolutely crucial experiments have never been performed. The history of these two ideas and the fact that most investigators have favored the concept of inherent automaticity are recorded, among other places, in the review of Cordier & Heymans (14).

(a) *The genesis of repetitive firing.*—By far the most concrete suggestion yet made concerning the nature of the repetitive firing of respiratory neurones is embodied in the theory of electrotonic control of nerve cell activity enunciated by Gesell (1) and applied to the respiratory center. Though a direct experimental approach to this problem has not been devised, several reports are current of experimental data which may be considered to afford indirect support to the hypothesis of electrotonic activation and control of nerve cells.

Eccles (15), studying synaptic potentials and transmission in the stellate ganglion and using curarized preparations to avoid the complications arising from the occurrence of spike potentials, found the ganglion cells becoming electrically negative to their axons following preganglionic stimulation. This negative potential (interpreted as synaptic potential) occupied a relatively long time interval compared with motor endplate potentials, resembled a catelectrotonic potential, and was capable of summation (during repetitive preganglionic stimulation) into a smoothed plateau. In partly curarized preparations, the negative "synaptic" potential became greater and spikes became superimposed upon the rising phase. Thus the appearance of impulses in the postganglionic axons was definitely associated with a negative electrotonic change in the cell body and there seemed little doubt that the latter was responsible for the former. When curare depressed the local negative potential produced by presynaptic impulses below about 20 per cent, no impulse was set up.

The association between axon impulses and a negative electrotonic potential apparently originating on cell bodies was evident also in the experiments of Prosser (16). In his single unit analysis of the heart ganglion discharge in *Limulus*, Prosser found, confirming Heinbecker (17), slow negative waves preceding and accompanying the axon spike discharges. The distribution of the waves among isolated segments of the ganglion corresponded well with the presence or absence of spontaneous rhythmicity and with the distribution of the large unipolar nerve cells believed to be the

pacemakers. Experimental conditions (e.g., bathing in isotonic sucrose) which enhanced or diminished the slow negative waves had a parallel effect upon the occurrence of axon spikes.

The experiments of Bullock, Burr & Nims (18), also performed upon the *Limulus* heart and its ganglion, were devised to test the hypothesis "that the frequency of firing of nerve cell bodies depends upon the DC electrical field in which they lie." Passage of direct current through the intact heart resulted in an abrupt, sustained, reversible increase in frequency of the heart beat and in changes in wave form of the electrogram. The site of action apparently was the ganglion, "more specifically the region of the pace-making cell bodies." The authors consider the abrupt character of the changes in activity and the nonaccumulating and promptly reversible character of the effects to argue against such factors as temperature rise or products of electrolysis as their cause and they consider them to be "a direct result of the electrical field itself."

The results of Gesell and coworkers (see below) on central humoral intermediation in respiratory control may be considered to offer strong indirect support for the theory of electrotonic control of nerve cell activity in general and for its use in interpreting the nature of the inherent mechanism controlling the repetitive firing of the neurones of the respiratory center.

(b) *The rhythmicity of the respiratory center.*—The paper of Pitts (19) upon "The Function of Components of the Respiratory Complex" is concerned with the other aspect of automaticity in the central controlling mechanism, namely, the rhythmic waxing and waning of the repetitive firing of the neurones of the center. Recording action potentials of individual phrenic neurones, Pitts studied the effects of vagus section and of carbon dioxide inhalation upon the respiratory act in "high decerebrate" and in "low decerebrate" cats. In the former, respiratory activity remained phasic after vagus section. In the majority of low decerebrate preparations vagus section was followed by continuous repetitive discharge of phrenic neurones (inspiratory cramp) which could be intensified by carbon dioxide inhalation or converted into approximately normal inspiratory discharges by rhythmic vagus stimulation. The results thus conform with those of Marckwald, of Lumsden, of Stella, and of Pitts, Magoun & Ranson. [See (1) and (19) for detailed bibliography and review of apneustic breathing and its implications.] Pitts therefore divides the central respiratory system into four functional subsidiaries: the respiratory center-motor neurone

system; the vagal inhibitory system; the brain stem inhibitory system; and other excitatory and inhibitory systems. The term "pneumotaxic center" is avoided in conformity with the view that "the brain stem inhibitory mechanisms" consist of "a number of reflex connections at various levels within the upper and middle brain stem the elimination of a sufficient proportion of which leads to inspiratory cramp." Pitts considers the activity of the respiratory center-motor neurone system in isolation to be continuous and that it is the addition of the vagal inhibitory system and the brain stem inhibitory system which imparts rhythmicity to respiration and provides the ground work for increase of rate as well as depth of respiration.

It is clear that this point of view makes respiratory rhythm entirely a matter of nervous integration and completely excludes the alternative possibility that respiratory rhythm is fundamentally an expression of inherent rhythmicity of individual pacemaker neurones which is modified and shaped by nervous integration. Because the issue is a deeply fundamental one, most observers will no doubt prefer to postpone final conclusions until conflicting evidence can be reconciled. Currently such conflicting evidence is represented by: (a) Pitts (19), confirming Marckwald (20), found that some of his vagotomized low decerebrate animals did exhibit sufficient rhythmicity of breathing to maintain life. (b) Nicholson & Hong (21) observed that, in unanesthetized decerebrate dogs, mid-pontine section and vagal block was followed by deep prolonged inspirations and that superimposed upon these inspirations there were rhythmic respirations at a normal frequency. Most significant of all, when considered in relation to the foregoing, was the observation that further section through the upper medulla (vagi sectioned or intact) "was followed by rhythmic breathing quite normal in type and frequency." These results certainly suggest that apneustic breathing is an expression, not of subtraction of an integrating force, but of superimposition of a distorting force upon the activity of the medullary half-centers. The potentialities of disturbed balance of the reflexogenic components of breathing as such a distorting force are strikingly demonstrated by the experiments of Gesell & Hamilton (22). (c) Meier & Bucher (23) studied the respiratory effects in the rabbit of combined vagotomy and brain stem section at various levels. The results included modification but not loss of respiratory rhythmicity following low pontine sections.

Gradation of intensity of inspiratory contractions.—The evidence bearing upon the pattern of the motor response governing the respiratory act was reviewed by Gesell (1) in 1940 and a central mechanism for its integration proposed. The basic mechanisms for grading the intensity of the inspiratory act were shown to be variations in twitch frequency of individual muscle units and recruitment and decruitment of individual units. Findings of different authors were at variance concerning the relative importance of these two factors. Adrian & Bronk (24) found no definite evidence for recruitment of phrenic nerve fibers in the rabbit and no evidence for increasing frequency of discharge during the progress of individual inspiratory acts. Gesell, Atkinson & Brown (25), on the other hand, found both acceleration of individual units and recruitment of new units to characterize the progress of individual respiratory acts of the dog, the two combined resulting in a progressive intensification of contraction to meet an increasing resistance to pulmonary inflation as inspiration progressed. Augmentation of both factors was responsible for hyperpnea. Pitts (19) found a similar pattern in the phrenic nerve discharges of the cat. In a recently reported study, Gesell & Atkinson (26) have extended their observations to the mouse, rat, rabbit, and horse, in all of which they found this same basic pattern, varying in the different animals only in intensity and duration. To quote, "Thus, the events transpiring in the prolonged inspiration of a horse are accelerated and compressed, without basic change, into the shortened inspiration of a mouse." This pattern for adjustment of muscular contractions is considered to be a primitive mechanism since it is found in insects, reptiles, and birds as well as in mammals (26). The evidence provided by the combined observations indicated, contrary to Adrian & Bronk, "that recruitment of reserve muscle units is a far more important mechanism of gradation of strength of contraction than is adjustment of twitch frequency."

THE CHEMICAL CONTROL OF BREATHING

The chemical stimulus of the respiratory center.—The seemingly well established concept (Winterstein; Gesell) that the activity of the respiratory center is regulated by its own intracellular hydrogen ion concentration has been subjected to repeated adverse criticism of late, notably by Nielsen (27), Krogh (28), Schmidt (29), and currently by Best & Taylor (30), who believe that the chemical stimulus is carbon dioxide acting, not as an acid, but

through some specific unknown action of its own. [See Gesell (31) for the history and analysis of this concept.] Without exception, the cited authors who recently have adopted this view give as their reason the results of Nielsen (27) derived from comparing the respiratory responses to ammonium chloride acidosis with the responses to carbon dioxide inhalation.

It is not within the scope of this paper to review the extensive experimental evidence supporting the hydrogen ion concentration theory nor to recount its advantages as a working hypothesis, the more so since these have all been thoroughly presented by Gesell in his several reviews and recently summarized and extended in their application to the expiratory center by Gesell, Moyer & McKittrick (32). However, in view of the fundamental nature of the point at issue, some attempt at critical evaluation of the evidence which has been interpreted as opposing the hydrogen ion concentration theory is demanded.

Nielsen's subjects experienced large increases of breathing (e.g., 10 liters per min.) associated with small diminution in the calculated pH of arterial blood (e.g., pH fall of 0.04 to 0.045 units) when breathing carbon dioxide. On the other hand, during ammonium chloride acidosis there were relatively small increases of breathing¹ (e.g., 0.7 and 0.3 liters per min.) associated with relatively greater changes in arterial pH (e.g., pH fall of 0.06 and 0.08). On the assumption that, in each situation, the change in pH of the arterial blood gave a quantitative indication of the change in cH of the cell interior, it was contended that the results demonstrated lack of quantitative correspondence, and hence no causal relationship between the magnitude of intracellular cH change and the magnitude of respiratory change. It was therefore concluded that carbon dioxide acted "specifically" upon the center and not by virtue of having raised the hydrogen ion concentration.

Obviously, the entire weight of this argument rests upon the assumption that arterial pH changes, under the experimental conditions which existed, were quantitative indicators of intracellular cH changes. One author (29) states in this connection, "it is inconceivable that the differences . . . could have been due to failure of the cells of the respiratory center to come to equilibrium with the

¹ Nielsen's subjects differed quantitatively in their responses to ammonium chloride from some others. For example, J. B. S. Haldane (33) experienced an increased pulmonary ventilation of more than 50 per cent (sitting) during similar degrees of chronic ammonium chloride acidosis.

arterial blood with respect to hydrogen ions." Such statements, though reasonable, may not be relevant. Certainly it would not be contended that equilibrium of intra- and extracellular concentrations means equality of concentrations. And granting that equilibrium can occur with unequal intra- and extracellular hydrogen ion concentrations, there is no specific reason for supposing that the inequality pertaining to equilibrium during hypercapnia would be identical with or proportional to the inequality pertaining to equilibrium during ammonium chloride acidosis.

On the contrary there are sufficient reasons for reluctance in making such an assumption. One of these arises from the experiments of Rous *et al.* (34, 34a) who used indicator methods to study the relative changes in pH of tissues and of arterial blood plasma in mammals. According to their plotted data, this method pointed to a much greater cH change in the tissues than in the blood during hypercapnia. On the other hand, following hydrochloric acid injection, which is comparable to ammonium chloride acidosis (33), the tissue changes were similar to or somewhat less than those occurring in the blood. Thus, speaking in terms of the arterial blood as a quantitative indicator of changes in tissue cH, according to these results it would fall short in the case of hypercapnia while telling the truth or exaggerating slightly in the case of ammonium chloride acidosis.

Despite known hazards attending the use of indicators for pH determinations in living tissues, the method is, nevertheless, the most direct which has been available and when existing evidence pertaining to the behavior of blood and tissue buffering systems is considered the results are not unreasonable. For example, if it be granted that the curve of carbon dioxide combining power of tissues generally is lower (35 to 39) and, more important, flatter (35, 39) than that of blood, it will be apparent that during hypercapnia, assuming equal increments of carbon dioxide tension in blood and tissue, that blood bicarbonate ion concentration will be increased more than will tissue bicarbonate ion concentration. But the increments of dissolved carbon dioxide and carbonic acid will be similar for blood and tissues, assuming similar solubility coefficients. Consequently the $[H_2CO_3]/[HCO_3^-]$ ratio, and hence the cH, will increase more in tissues than in blood. It must be admitted that insurmountable uncertainties bar further reasoning should it be attempted to predict the final equilibrium which may occur in hypercapnia. Thus some investigators, such as Henderson & Haggard

(40), maintain that bicarbonate migrates from tissues into blood during carbon dioxide inhalation, others, including Shaw & Measer (41), that bicarbonate migrates from the blood into tissues, while still others, represented currently by Rosenbaum (42), maintain that the tissue cells of man are impermeable to the bicarbonate ion.

There are additional reasons for questioning a quantitative correspondence between blood and tissue cH changes during ammonium chloride acidosis. Katz & Banus (43) found that some types of tissue (e.g., muscle) do not contribute even in small degree to the buffering of fixed acids (hydrochloric acid) liberated into the blood stream. The finding of Rous *et al.* (44) that the cH of "parenchymatous tissue" cells was changed very little, if at all, when mineral acids were added to the blood, whereas "matrix tissues" (e.g., connective tissues and cartilage) did experience such change must invite wonder as to the category in which respiratory neurones may belong. Jacobs (45) found ammonium hydroxide among bases occupying much the same position as that of carbonic acid among acids in its ability to penetrate cell membranes and he demonstrated alkaline changes within cells immersed in acid solutions of ammonium chloride. A further potentially complicating factor is embodied in the suggestion (46, 47) that the ammonium radical may have a specific action upon nerve cells.

Leaving the question of whether the results of Nielsen do actually constitute evidence against the cellular cH theory, it seems pertinent to examine the alternative theory (specific action of carbon dioxide) in the light of the same experimental results. While there have been few suggestions on the part of the adherents of this theory as to how carbon dioxide might exert its specific action,² it seems reasonable to assume that its effectiveness as a stimulus would be in proportion to its molecular concentration. Granting this, difficulties arise at once in the application of the theory to the dyspnea of acidosis (ammonium chloride or other) for there can be no doubt that in this situation the molecular concentration of carbon dioxide and of its salts is diminished in cells, tissue fluid, and blood alike. Yet breathing is increased rather than diminished. Nielsen proposed the accessory theory that in

² Schmidt (29) suggests that the carbon dioxide molecule acts by hastening oxidative reactions within the respiratory neurones. For the body as a whole, on the other hand, Campbell (85) and also Gesell, Krueger, Gorham & Bernthal (38) demonstrated that increased carbon dioxide tensions diminish oxidations and the total energy output.

ammonium chloride acidosis the excitability of the center to carbon dioxide is increased. How acidosis would increase the excitability of the center to carbon dioxide was left unanswered. As Gesell has pointed out (48), this latter difficulty is nonexistent if the intracellular cH theory is retained, for acidosis due to alkali deficiency means a smaller absolute as well as relative value for the denominator of the $[H_2CO_3]/[HCO_3^-]$ fraction. Any given absolute increase in carbon dioxide must then represent a greater relative increase, and the value of the ratio, and hence the cH, must rise more as a result during acidosis than under normal conditions.

Indirect support for the intracellular cH theory is to be found in the results of Moyer & Beecher (49). In his original exposition of this concept (31), Gesell postulated two interdependent effects of oxygen lack upon the respiratory center, "a harmful effect upon the vegetative function, and an excitive effect upon the activity of the center." Since the discovery of the chemoreflexes, the revelation of a predominantly depressing direct effect of hypoxia upon the center has been assumed to indicate that the central excitatory effect of the increased intracellular cH was masked or overbalanced by the effect of diminished oxidations upon the vegetative function. If this is true, it should be possible to demonstrate the excitatory action. This was done in the experiments of Moyer & Beecher in which lightly anesthetized dogs deprived of known chemoreceptive reflex drive mechanisms exhibited a significant sustained respiratory stimulation as a result of oxygen scarcity in inspired air. The pattern of the reactions suggested the operation of two opposing influences with a shifting balance between them, for the respiratory stimulation was preceded by a long latent period associated with depression of breathing. In all experiments there was a postanoxic hyperpnea, greater than that attained during hypoxia, and this was interpreted as meaning that, under the influence of increased available oxygen during recovery, the threshold of the center to hydrogen ions decreased more rapidly than did the cH of the center. The authors concluded that apparently decreased oxidations within the center constitute a most important limiting factor of respiratory adjustments to changes in central cH.

Comroe (13) believes that his recently reported experiments provide evidence against the "acid" hypothesis. In these experiments the procedure employed was the injection of small quantities (1 to 2 c.mm.) of chemical solutions directly into the region of

the respiratory center of cats. Injections of carbon dioxide-bicarbonate mixtures were followed often by immediate hyperpnea, whereas acids (carbonic, lactic, and hydrochloric) rarely stimulated. Comroe suggests that the bicarbonate ion may be a very important factor in the control of respiration. That the acid solutions rarely stimulated is, perhaps, not surprising if one considers that their injection results in the liberation of a minute quantity of highly mobile carbon dioxide in a region of sparsely distributed neurones (reticular formation) and exceedingly numerous capillaries. With an abundance of avenues for escape of rapidly diffusing carbon dioxide into the blood stream the period of raised $p\text{CO}_2$ in the immediate environment of the respiratory neurones must have been very short indeed. On the other hand, after injection of carbon dioxide-bicarbonate mixtures, the relatively slow diffusion of the bicarbonate ions would tend toward permitting them to remain in the environment of the neurones for the time necessary effectively to exert their action of driving carbon dioxide (carbonic acid) across the cell membranes or damming it back there.

Humoral intermediation in central nervous control of respiration.

—According to the concept stated by Gesell, Brassfield & Hamilton (50, 51) of an "acid-humoral" mechanism for nerve cell activity and the regulation of respiration, variations in cH may control the longevity of physiologically deposited acetylcholine, an increased cH prolonging and a decreased cH shortening the life span of acetylcholine liberated at synapses. Because of apparent misunderstanding on this score [Comroe (13), p. 495], it should be noted that, in applying the "acid-humoral" concept to the integration of the activity of the respiratory center, Gesell, Brassfield & Hamilton took care to state that they did not suggest the elimination of the direct stimulating action of cH on nerve cells and that what they proposed was an additional mechanism in which increasing cH would exert an indirect stimulating control.

Because this concept cannot be applied to the activities of the central nervous system unless humoral intermediation itself is first established for the normal activity of the centers, Gesell and his coworkers have undertaken the study of the latter phenomenon in relation to the respiratory act. In the paper of Gesell, Hansen & Worzniak (52) it was shown that acetylcholine injected intra-arterially or applied to the floor of the fourth ventricle in dogs with denervated carotid and aortic chemoreceptors produced essentially a normal hyperpnea and that the response was graded in accord-

ance with the concentration of acetylcholine at the center. Potentiation of the effects of impulses impinging on respiratory nerve cells was shown (a) by the exaggeration of the responses to Hering's nerve stimulation or to lung inflation during acetylcholine injection, and (b) by a difference in the pattern of the hyperpnea resulting from acetylcholine injection with blocked and with intact vagi (frequency of breathing greater and amplitude less in the latter case). Physostigmine potentiated the stimulating action of extrinsic acetylcholine deposited on the floor of the fourth ventricle and it also potentiated the action of intrinsic acetylcholine as indicated by the occurrence of hyperpnea following intracarotid injection (physostigmine) and by a greater and more prolonged reflexogenic response to stimulation of the superior laryngeal nerve and of Hering's nerve. The activity of both half centers was involved in the potentiation by physostigmine. A further point, brought out in the paper of Gesell & Hansen (53), is that the effects of physostigmine may be duplicated by slowly injected extrinsic acetylcholine. The authors believe it a fair assumption that a mechanism of humoral intermediation of nervous integration, such as that demonstrated for the respiratory act, may function in all nervous integrations.

The effects of atropine, presented in the paper of Gesell & Hansen (53), provide additional evidence favoring humoral intermediation in central integration of the respiratory act. Intravertebral arterial injections of atropine (with carotid denervation and double vagotomy) caused diminution, but not abolition, of the reflexogenic hyperpnea produced by stimulation of Hering's nerve. Atropine was shown also to reverse each qualitative change in breathing set up by physostigmine, and a similar antagonism between atropine and the action of injected (extrinsic) acetylcholine was demonstrated. The authors therefore believe that atropine is capable of exercising a powerful anti-acetylcholine and anti-physostigmine action in the nerve cells of the central nervous system and call attention to the fact that their findings, along with those of Miller, Stavraký & Woonton (54), corroborate those of Marrazzi (55) in peripheral ganglia and make the observation general for all nerve cells. [See Garrey (56), however, for an opposite action of atropine on the nerve cells of the cardiac ganglion of *Limulus polyphemus*.]

In connection with the proposed neurohumoral concept of respiratory control, Comroe (13) invited special attention to his own

finding that 128 injections of acetylcholine directly into the region of the respiratory center produced no clear cut instance of respiratory stimulation. While no attempt was made to account for the contrasting results, it would seem that the most conspicuous way in which Comroe's experimental conditions differed from those of Gesell and coworkers was the much greater localization of the acetylcholine applied. It has been amply demonstrated for pacemaker structures in general [e.g. Gaskell (57) for the heart; Garrey (56, 58) for the cardiac ganglion of *Limulus*] and for the respiratory center in particular [Brookhart (4); Pitts, Magoun & Ranson (2); Pitts (8); Comroe (13)] that the pacemaker function can be relocated to any chosen point within the pacemaker structure by appropriate localized stimulation and Garrey (56) has demonstrated that this can be done by punctate application of acetylcholine itself to the cardiac ganglion of *Limulus*. In all such cases the one necessary condition, presumably, is that the cell or cells which are to take over the pacemaker function be incited to more intense activity than the existing pacemaker. In the experiments of Comroe the acetylcholine may very well have excited in the localized regions in which it was applied even though the resulting localized activity failed to exceed in intensity that of the pre-established pacemaker neurones in the respiratory center and so have failed to produce a coordinated hyperpnea.

In addition to providing evidence bearing upon humoral intermediation in central nervous activity, Gesell and coworkers believe that the respiratory response to acetylcholine and physostigmine support the concept that the dominant role in nervous integration is exercised by neuroarchitectural patterns, e.g., the electrotonic theory of nerve cell activity, and of synaptic drive and its corollary concept of excitation and inhibition determined by "geographical" impingement of impulses upon the nerve cell body as described by Gesell (1) rather than by temporal patterns of sensory impulses. This support is derived from the observation that acetylcholine injection, "an exceedingly crude stimulation which has but two attributes—quantity and duration," produced the highly coordinated activity which normal hyperpnea represents (a composite of about ten integrated changes in a single respiratory cycle). The responses to physostigmine, though highly complex (Gesell & Hansen), were interpreted upon a similar basis. The resulting "humoro-electrical" theory is summarized by Gesell & Hansen (53) as follows:

activation of nerve cells transpires in two stages, humoral and electrical. Impulses impinging on the nerve cell release the neurohumor. Acetylcholine by virtue of its rate of destruction pools at the dendrites and cell body and provides an adjustable electrochemical voltage, the intensity of which is determined by the size of the pool. A resulting continuous current leaves the neurons at the axon hillock and fires the neuraxon at a frequency proportional to its intensity.

The chemoreflex component of respiratory control.—The existence of the carotid and aortic chemoreflex mechanisms, the identity of the external agents capable of stimulating them, and their dominating role in the adjustments to severe hypoxia are firmly established. For reviews see (1, 48, 59, 60, 61, 126). The role of the chemoreflexes in relation to the finer adjustments of breathing under less stringent circumstances continues to be variously interpreted. Schmidt & Comroe (60, 61, 62) have vigorously urged that the function of the chemoreceptors is largely limited to "emergency situations" and "that the part played by chemoreceptor reflexes in adjusting pulmonary ventilation to the requirements of the body must be negligible under normal conditions." A number of other workers, among whom may be mentioned Heymans & Bouckaert (59), v. Euler & Liljestrand (63, 64), Gesell (1, 48) and, more recently, Gollwitzer-Meier & Lerche (65), have ascribed to the chemoreceptors a less limited participation in respiratory adjustments.

Because of continuing differences concerning a fundamental question and in order more effectively to evaluate several pertinent studies (64 to 68) which have recently become available, it is necessary to review critically some of the earlier experimental work. In reviewing this material evidence will be sought upon three main points, all of them controversial at the present writing and all of them bearing fundamental relationship to the question under consideration.

(a) *The threshold of the chemoreceptors to hypoxia and hypercarbia.*—The recording of Hering's nerve action potentials (69, 70) is the most direct method for estimating chemoreflex thresholds. v. Euler, Liljestrand & Zotterman (70), using preparations in which only very few "chemical fibers" were left intact, found new axon potentials appearing as soon as the oxygen saturation of the blood fell below about 96 per cent and the impulses increased in frequency in approximately linear proportion to the oxygen desaturation as lower blood oxygen tensions were induced. These results indicate clearly that the chemoreceptors increase their activity as soon as the arterial oxygen tension falls below normal values

and place the threshold oxygen tension at 85 mm. Hg³ or a little above (based on characteristics of human blood, pH 7.34). The response might have begun at a higher oxygen tension had not the carbon dioxide tension been subnormal due to artificial hyperventilation.

For carbon dioxide tension under conditions of pure oxygen inhalation the threshold was found in the neighborhood of 30 mm. Hg, the results being in substantial agreement with those of Samaan & Stella (69).⁴

The results of the axon potential studies agree well with the results of less direct procedures. In experiments designed to portray simple chemoreflex respiratory and vasomotor reactions neither masked nor exaggerated by other factors, Bernthal (73) found evidence of definitely increased chemoreceptor activity when the oxygen tension in the arterial blood supplying the carotid body was lowered from 89 mm. to 79 mm. Hg and there were reasons for believing that the threshold oxygen tension lay at a level considerably above this (approximately 100 mm. Hg).⁵ The results thus indicated chemoreceptor activity at eupneic levels of arterial

³ According to the recent studies of Cullen and Cook (71), normal human arterial pO_2 averages 72 mm. Hg.

⁴ Schmidt & Comroe (61) consider it improper to use the results of such studies as evidence of chemoreceptor activity, arguing that the electrical activity may have originated elsewhere. However, if the signals are ascribed to sources other than chemoreceptors it becomes difficult to explain the facts that they disappeared upon hyperventilation with oxygen and upon administration of ammonium hydroxide and increased in the orderly manner described above in response to change in oxygen and carbon dioxide tensions and to other chemical agents to which chemoreceptors are known to respond. It is true, as v. Euler *et al.* suggested in their original study and later definitely established (66), that impulses from small pressure fibers may be recorded in Hering's nerve in the cat. However, unlike the impulses ascribed to chemoreceptors, they did not disappear upon hyperventilation with oxygen or upon administration of alkali and were associated with the systolic rather than with the intersystolic intervals of arterial blood pressure.

It seems unlikely, too, that the impulses were of sympathetic origin (60), especially since the impulse frequency of Hering's nerve fibers (even allowing for several having been recorded simultaneously) rose to values very much higher than that reported for sympathetic motor nerve cells (72).

⁵ In discussing this paper, Schmidt & Comroe (60) evidently mistook percentage of gas in equilibrating air for volumes per cent in blood and so erroneously concluded that these results agreed with their own findings according to which chemoreceptor sensitivity is much lower (threshold oxygen tension a little less than 50 mm.). In order to avoid further confusion, the values are presented here in terms of calculated oxygen tension rather than in percentages as they appeared in the original report.

oxygen and carbon dioxide tensions and, since such activity could be lessened either by raising the oxygen tension above eupneic levels or lowering the carbon dioxide tension below such levels, it was concluded that both factors operated in maintaining the implied tonic chemoreceptor activity.

(b) *Tonic chemoreceptor activity as a respiratory drive.*—That the tonic chemoreceptor activity so indicated has its counterpart in reflex respiratory drive of significant though moderate proportions has been demonstrated by evidence of several different kinds, only part of which can be cited here.

To evaluate eupneic chemoreflex respiratory activity, chemoreceptor influence may be suppressed and the effects upon breathing measured. Bernthal & Weeks (74) used this procedure, cooling the otherwise normal arterial blood which perfused the isolated carotid bodies. Diminished breathing of as much as 34 percent indicated definite tonic respiratory stimulation of carotid body origin.⁶ It was recognized, however, that the use of anesthesia may have accentuated the magnitude of this stimulation (75) and no attempt was made to apply the results quantitatively to normal unanesthetized individuals.

Of special significance therefore are the recently reported experiments of Watt, Dumke & Comroe (68) upon normal unanesthetized dogs. Pure oxygen inhalation, designed to remove all hypoxic stimulation of chemoreceptors, led to a diminution of breathing varying from 11 to 31 per cent and the authors concluded that some chemoreceptors must be continually activated by the usual degree of oxygen unsaturation of the arterial blood at sea level (the average arterial pO_2 in their experimental animals was 74 mm. Hg). Since a considerable degree of chemoreflex activity was apparently already operative during eupnea, the experiments indicate, in harmony with others already cited, a chemoreceptor threshold for diminishing oxygen tension at some level higher than

⁶ The results of Bernthal & Weeks were confirmed by Schmidt, Comroe & Dripps (76), but inasmuch as the respiratory depression also occurred upon cooling of a perfusing fluid of pH 7.5, carbon dioxide free and saturated with oxygen, these investigators suggested that something other than chemoreceptors was being cooled. Bernthal & Weeks emphasized the importance of preventing the temperature change from involving the intracranial circulation where temperature changes *per se* (77, 78) give rise to respiratory reactions. Since the report of Schmidt *et al.* does not indicate what measures, if any, were taken for controlling this potential source of error, it is impossible to judge whether or not it was responsible for the nonchemoreceptor reactions noted by them.

that of normal arterial blood.⁷ Watt, Dumke & Comroe call attention to the tendency in some of their animals for recovery of breathing to occur during the oxygen inhalation and they regard this as evidence that the tonic chemoreceptor activity demonstrated was not essential for the maintenance of normal respiratory activity. It may be remarked that the tendency for recovery of breathing would be expected to result from carbon dioxide accumulation in the tissues (diminished pulmonary ventilation plus impaired transport of carbon dioxide due to diminished reduction of oxyhemoglobin) and from the central stimulating action of raised oxygen tension *per se*. But it may be questioned whether the new situation, with its altered blood and tissue carbon dioxide tensions, represents normal respiratory activity.

The importance of carbon dioxide in chemoreceptor stimulation has been questioned because a unit change of environmental carbon dioxide tension is much less effective in eliciting reflex response than is a unit change in oxygen tension. In a sense it is impossible to consider either carbon dioxide or oxygen lack as separate stimuli for, assuming that intracellular cH is the actual stimulus, the reaction to one will always be conditioned by the presence of the other and their effects at the chemoreceptors are additive as has been experimentally demonstrated by Winder (79).

That eupneic levels of arterial carbon dioxide tension do actually contribute to tonic chemoreflex respiratory stimulation was shown by the experiments of v. Euler & Liljestrand (64). Noting that section of Hering's nerves was followed by a marked rise in resting alveolar carbon dioxide tension and by depression of breathing, and noting further that the effect, though lessened, was not abolished by pure oxygen inhalation, these authors concluded as earlier (63) "that the carbon dioxide tension of the blood under physiological conditions stimulates respiration, not only by direct action on the respiratory center, but also reflexly over the sinus mechanism." The conclusion applied to both dogs and cats and to decerebrate as well as anesthetized animals.

The well controlled experiments of Gollwitzer-Meier & Lerche (65) provide further aid in evaluating the effects of carbon dioxide. Comparing central and reflex respiratory responses to alterations of arterial carbon dioxide tension, these authors found in harmony

⁷ Moyer & Beecher (104) found depression of breathing by oxygen inhalation in only two out of eight anesthetized dogs.

with many others [not, however, including Heymans & Bouckaert (59)] that the center was responsive to smaller changes in carbon dioxide than were the chemoreceptors. The threshold change for reflex respiratory response was found to be about 6 mm. Hg, i.e., a rise from 31 to 37 mm., corresponding to a pH decrease of 0.055. The authors state: "Die Funktion der endosinualen Chemoreceptoren beschränkt sich also nicht auf Notstandsbedingungen, wie Comroe und Schmidt annehmen. Wir müssen aber Comroe und Schmidt, entgegen Heymans, darin Recht geben, dass die endosinualen Chemoreceptoren nicht empfindlicher sind für den Kohlenäurereiz als das Atemzentrum."

Gesell, Lapidès & Levin (80) studied the effect of repeated withdrawal of chemoreflex support (by cold block of Hering's nerve) during progressive hypercapnia. Their findings for mild hypercapnia are in harmony with those of others already cited. However, as hypercapnia became more intense, withdrawal of reflexogenic support caused a diminishing absolute reduction in breathing until at 5 to 6 per cent carbon dioxide in inspired air there was no effect whatever. The hyperpnea of high grade hypercapnia was therefore concluded to be purely centrogenic.

Though not complete, the experimental evidence so far presented establishes a reasonably sound basis for the belief that the chemoreceptors are moderately active under eupneic conditions, that both the oxygen and the carbon dioxide tensions characteristic of arterial blood during eupnea are factors in maintaining this activity, and that the chemoreceptor activity results in definite respiratory stimulation.

(c) *The response of the chemoreflex mechanism to deviations from eupneic conditions.*—Much recent discussion and experimental work has centered about the question as to whether deviations from eupneic conditions short of emergency situations can call forth additional chemoreflex activity of significance or importance in respiratory control. Where the dividing line between "emergency" and "ordinary" situations lies and what constitutes significance and importance in respiratory adjustments are decisions which the individual reader must make for himself. However, evidence can be cited, aside from that implicit in the experimental results already considered, which has a bearing upon these questions.

An illuminating example is the reaction of man to progressive hypoxia as revealed by the experiments of Ellis (81) and of Lutz & Schneider (82). Although the first of these is often cited (60, 61)

as proof that man's respiratory adjustment to hypoxia does not begin until the oxygen percentage of inspired air has fallen to 18 per cent, Ellis' own observation was different for he stated, "Although the individual minute to minute data for respiratory volume cannot be given here, they showed when plotted as curves, a distinct upward trend in every case after the first or second minute of rebreathing, suggesting that the actual increase in respiratory volume began earlier than the fifth minute and at an oxygen per cent higher than 18.1." Lutz & Schneider, reporting similar studies simultaneously with Ellis, came to a similar conclusion and, in addition provided data concerning alterations in alveolar air which are pertinent for they point to chemoreceptor activity beyond that measured by increased respiratory volume alone. At 650 mm. atmospheric pressure, corresponding to an altitude of 4,000 feet or to 18 per cent atmospheric oxygen at sea level, they found lowered alveolar carbon dioxide pressures in all their subjects, in some cases as much as 6 and 7 mm., but averaging 2.7 mm. This finding implies well developed chemoreceptor activity at that level (650 mm. Hg) for, regardless of whether the reduced alveolar carbon dioxide tension was due to initially increased pulmonary ventilation, as Lutz & Schneider thought, or whether it was due to the diminished barometric pressure *per se* (83), the consequent reduction in chemical stimulus at the respiratory center must have resulted in a secondarily lessened minute volume of breathing⁸ had not some other factor compensated. Presumably that factor was increased chemoreceptor activity and this explanation is borne out by the experiments of Gesell, Lapidès & Levin (80) to be described presently.⁹ Thus, not only must the chemoreceptors have begun their response to hypoxia at an oxygen per cent higher than 18.1, as Ellis stated, but at 18.1 per cent they had increased their activity in sufficient degree to offset a definite diminution in the chemical stimulus of the respiratory center. To the writer this appears to be an example

⁸ According to Haldane (84), often quoted in this connection, an increase in alveolar carbon dioxide of 1.5 mm. Hg in man may result in a doubling of pulmonary ventilation.

⁹ To explain the absence of diminished minute volume of breathing under such circumstances, it might be assumed that the excitability of the center to carbon dioxide is increased. [See Nielsen (27) for bibliography of this concept.] The explanation offered here, more in accord with experimentally demonstrated facts, is that excitation, not excitability, is increased and that the increased excitation arises from the complementary action of the chemoreceptors stimulated by diminished oxygen tension.

of participation of the chemoreceptors in the "finer adjustments" of breathing. Certainly, considering the shape of the oxyhemoglobin dissociation curve, the oxygen want of the tissues cannot be great during 18 per cent oxygen inhalation. Yet the incipient diminution of oxidations is already being offset (38, 85, 86) by diminishing acidity through lowered carbon dioxide tension.

Though probably useful, a reaction such as this surely is not indispensable or even essential to the organism when oxygen deficiency is mild. It does, however, represent an early and rather delicate adjustment of the respiratory control mechanism to changing conditions and it is one, moreover, which may pass unnoticed if changes in minute volume of breathing alone are measured.

That it is the chemoreceptors which are responsible for the fine adjustments of the respiratory mechanism to mild hypoxia is clearly shown by the experiments of Gesell, Lapides & Levin (80) who studied the relative contributions of reflexogenic and centrogenic factors under varying conditions of oxygen supply. Blocking Hering's nerves during inhalation of 40 per cent oxygen removed a definite but small element of respiratory stimulation. Switching from 40 per cent to 19.6 per cent oxygen inhalation produced a definite augmentation of breathing. But thereupon blocking of chemoreceptor signals reduced breathing sufficiently to more than offset this augmentation and revealed that the remaining centrogenic breathing was definitely less than it had been during 40 per cent oxygen inhalation. Thus, as in the experiments on man, the reflexogenic (chemoreceptor) factor was augmented sufficiently not only to cause the observed increase in breathing but, in addition, to offset a diminution of the central component. It is worthy of emphasis again that had the contribution of the chemoreceptors to respiratory control been judged merely by the amount of increase in breathing in the absence of nerve block it would have been grossly underrated.

As more severe oxygen want was imposed in these experiments, the central component diminished progressively and the reflexogenic component ultimately assumed complete responsibility for the hyperpnea, in which situation elimination of chemoreceptor support resulted in apnea.

Suggestive of another mode of chemoreceptor participation in respiratory adjustments of every day life were the observations, confirming those of King (87), of their relationship to the apnea resulting from hyperventilation with room air. Blocking of Her-

ing's nerves caused threefold prolongation of hyperventilation apnea in one example. In another, overventilation insufficient to abolish breathing at all when Hering's nerves were functioning produced apnea of a minute's duration when they were blocked. Thus the center was enabled to accomplish a much earlier resumption of activity when its own reduced drive was complemented by chemoreceptor drive. Eventually, following hyperventilation, the respiratory center will rebuild its own chemical stimulus by reac-cumulating carbon dioxide but in the interval required for this it must, unaided, inevitably encounter increasing oxygen lack (since oxygen stores are not augmented during hyperventilation in proportion to the depletion of carbon dioxide) and this it is ill equipped to endure. Chemoreceptor support relieves the center of taking this risk by substituting its own drive (tonic activity plus early response to hypoxemia) for that temporarily lacking at the center. The potentiality for such a state of affairs is inherent in every situation in which the center is driven by agencies outside itself.

Though the interrelationships between chemoreflex and other components of respiratory control are at present incompletely understood, the potentialities for sensitive coordination and intimate cooperation in finer adjustments under normal conditions seem considerable if the evidence so far presented can be relied upon. The properties of the chemoreflex mechanism which make its participation in normal respiratory control seem probable might be summarized as follows:

(a) Its activity can be modified by alterations of either carbon dioxide or oxygen tensions and the chemoreceptors are so constituted that the influence of these two factors can be summed (probably through the common denominator of alterations in intracellular CH).

(b) Its threshold to these stimuli is such that it is already active at eupneic levels of oxygen and carbon dioxide tension, and in sufficient degree to account for a measurable fraction of the minute volume of eupneic breathing.

(c) The mechanism responds in a sensitive manner to deviations from these levels, especially where oxygen is concerned. In the latter case the relative quantitative response to variations in tension at various levels seems to be such as to coordinate chemoreceptor response to the change in oxygen content of the blood as reflected in the oxyhemoglobin dissociation curve.

(d) The chemoreflex mechanism is so constituted that it is capa-

ble of working in close harmony with the respiratory center and in so doing it may display great adaptability. Always effective in some degree except under conditions of high grade hypercapnia, its relative share of the total respiratory drive may vary from one extreme to the other depending upon prevailing circumstances. It may supplement the activity of the center (as in mild hypercapnia or in other forms of acidosis), or its action may complement that of the center, either continuously (as in hypoxia) or temporarily, following situations in which excessive external drive has resulted in depletion of direct chemical stimulation at the center (hyperventilation apnea). The complementary action is made possible by the chemoreceptors' capacity for sensitive response to hypoxia. It protects the respiratory center and other vulnerable tissues from potentially damaging hypoxia not only by resisting the development of hypoxia itself but also, if hypoxia supervenes, by supporting oxidations through diminution of carbon dioxide (lessened cH).

It is suggested that recognition of these properties and of the capacity for participation in every day adjustments of breathing which they imply may speed eventual understanding of those adjustments.

In presenting this point of view it is emphatically not intended to imply that chemoreflex function is indispensable, except under special conditions in which the center is deprived of direct chemical excitation either through depressed excitability or through diminution of chemical stimulus. On the other hand, the idea that chemoreflex participation in respiratory control is limited to these situations in which it is indispensable seems to us not to be in accord with experimentally demonstrated facts. We visualize instead a smoothly graded scale of chemoreflex participation ranging from their relatively modest contribution during eupnea to their completely dominant position in severe hypoxia and during certain types of anesthesia. It is suggested that the phenomenon of compensatory reactions for chemoreceptor loss under nonemergency conditions is an argument against indispensability but not against usefulness.

The opposing view of Schmidt and collaborators (60, 61, 62) that the role of the chemoreceptor reflexes in respiratory control is limited to what are designated as "emergency situations" has been noted earlier. It is now proposed to examine such positive experimental evidence as has been offered in support of this concept.

Comroe & Schmidt (88) employed perfusion experiments to

test the chemoreflex respiratory response to hypoxia. They were unable to demonstrate a response to anoxemia of less than 4 volumes per cent and they later (60) interpreted this to mean that reflex hyperpnea began at an arterial oxygen tension of a little less than 50 mm. Hg. The reasons for the low sensitivity in these experiments can only be guessed. However, in deciding whether these negative results invalidate the finding by others (70, 73, 80) of a much higher sensitivity, consideration should be given to the facts that only one carotid body was used, that the preparation was one requiring unusually extensive dissection and manipulation of the carotid body, and that the use of an artificial perfusate (Locke's solution) in place of blood during parts of the experiment may have modified the sensitivity of the chemoreceptors despite their ruggedness.

In the only other instance of which we are aware (67) in which Schmidt and collaborators have produced actual experimental results bearing upon chemoreceptor sensitivity to hypoxia, the whole animal was exposed to lowered oxygen tension and the chemoreceptor threshold was then judged by the smallest degree of hypoxemia associated with 10 per cent increase of breathing. By means of this test the threshold was set at an oxygen tension of 50 to 55 mm. Hg. But the soundness of the criterion used is certainly open to question. For the activity of respiratory center as well as chemoreceptors may be altered by hypoxia—moreover, in opposite directions; both were subjected to it; yet the resultant respiratory reaction was taken to represent the response of one (the chemoreceptors) alone. Other data from these experiments reveal the error clearly enough. For example, Dog 1, breathing 12 per cent oxygen, gave no evidence of chemoreceptor response according to this criterion. Actually, however, the presence of the chemoreceptors had prevented a depression of breathing of at least 20 per cent and a fall of arterial pO_2 of at least 7 mm. Hg as shown by the subsequent reaction when low oxygen was inhaled without benefit of chemoreceptors. Again, animals without chemoreceptors succumbed when breathing an oxygen mixture (12 per cent) which in intact animals produced only just measurable evidence of chemoreceptor activity at an arterial pO_2 of 55 mm. Hg. Thus, this test may fail to detect chemoreceptor activity until it has reached such proportions that its absence may result in death.

The same error is inherent in the reasoning which led to the assertion (60, 62) that 67 mm. of oxygen tension is "the greatest

sensitivity to anoxemia that we have any right to expect in the chemoreceptors of man," based upon the commonly made observation that increased breathing does not begin until the oxygen of inspired air falls to 18 per cent. It has already been shown that under these conditions well developed chemoreceptor activity may be masked by concomitant diminution of direct chemical stimulation at the center.

Chemoreceptor contribution to hypercapnic hyperpnea was evaluated by Schmidt and coworkers (67, 89) by comparing the hypercapnic responses before and after chemoreceptor deafferentation. During the interval necessarily elapsing between the comparative tests the resting breathing increased markedly (as much as 89 per cent in one set of experiments and 66 per cent in another). Inasmuch as a suggested cause for this was partial recovery from the anesthetic (67), this unavoidably raises the question whether the tests were really comparable, for it is not improbable that the increase in sensitivity of the center to carbon dioxide which recovery from anesthesia entails (75, 90) might mask or even overbalance the potential results of chemoreceptor removal. In any event the absence of chemoreflex stimulation could not have accounted for the markedly shortened onset time and the markedly exaggerated hyperpnea which occurred during the second of the pairs of comparative tests and some powerful extraneous factor must obviously have been at work. It is not clear, therefore, upon what grounds the data from these experiments were presented as quantitative evidence of nonparticipation of chemoreflexes in hypercapnic hyperpnea nor why they have since been advanced (61) in opposition to the findings from other experimental procedures (80) free of the technical defects noted.

It may be remarked, however, that fundamental differences in approach to respiratory control as well as questions of validity of experimental evidence are concerned in the different interpretations of chemoreceptor function. Granting, as the preponderance of experimental evidence seems to indicate, that the respiratory center is more powerful and sensitive in its response to carbon dioxide than are the chemoreceptors, the contribution of the latter may still have physiological significance if reflex and central responses are viewed as separate components which may be added and the sum of which, along with other factors, determines the total responses (80). If, on the other hand, the respiratory control mechanism is thought to be so organized that the total response is deter-

mined only by the more sensitive and powerful of simultaneously acting influences, then the center would be considered all important and the reflex factor insignificant in the response to carbon dioxide.

Of the experimental evidence put forth by Schmidt and collaborators concerning eupneic chemoreflex activity, only the recently reported results (68) upon unanesthetized dogs need be considered since, presumably, they take precedence over the different results presented earlier from Schmidt's laboratory (67, 89). One aspect of these results has already been discussed. In this same paper, Watt, Dumke & Comroe presented, as additional evidence against the participation of chemoreflexes in the maintenance of normal respiratory activity, the absence of depression of resting breathing in their unanesthetized animals following chemoreceptor denervation. In evaluating this observation consideration should be given to the following facts: (a) The denervation interrupted pressure receptor (respiratory inhibitory) pathways and this would tend to mask possible effects of chemoreceptor denervation. (b) The experiments of several investigators (91 to 94) indicate that pressoreceptor denervation is followed by increased metabolic rate in dogs, and this would tend to mask possible effects of chemoreceptor denervation. (c) The comparative measurements before and after denervation had to be made at widely separated intervals upon unanesthetized animals. It would be a precarious undertaking to decide whether, in addition to these several factors, a chemoreflex factor also entered into the determination of the experimental results.

Often presented (61, 62) as proof that tonic chemoreceptor activity is absent in man is the observation (95) recently confirmed by Watt, Dumke & Comroe (68) that in man oxygen inhalation may increase breathing. But inasmuch as the respiratory center as well as the chemoreceptors was exposed to the high oxygen tension during such inhalation, the result may only mean that in man the central stimulating action is sufficient to overbalance the effect of chemoreceptor inactivation. The tendency for the central stimulating influence to mask the chemoreceptor inactivating factor is clearly suggested in the experiments of Watt, Dumke & Comroe, for the deafferented dogs which exhibited the most marked respiratory stimulation during oxygen inhalation were also the dogs which before denervation had exhibited the greatest tendency for recovery from the respiratory depressing effects of the same procedure.

THE HYPERPNEA OF MUSCULAR EXERCISE

The hyperpnea of muscular exercise is probably the most frequently used and powerful adjustment of which the respiratory system is capable and at the same time it has been considered the least well explained by current concepts of respiratory control. Perhaps the least which may be demanded of an explanation of exercise hyperpnea is (*a*) that it identify the stimulus or stimuli which bring about the hyperpnea, and (*b*) that it account for the well established fact that, for work below crest load in intensity, pulmonary ventilation bears a linear relationship to the oxygen absorption after a steady state has been reached.

That explanations involving purely chemical control mechanisms are not adequate is amply demonstrated by the repeated statements in textbooks and reviews to the effect that in moderate exercise breathing may be markedly increased without augmentation of known chemical respiratory stimuli. Attempted explanations involving nonchemical control mechanisms have been few, partly because of the potential difficulty in accounting for the obvious adjustment of breathing to chemical needs, but chiefly because the existence of such mechanisms of sufficient power has not been considered well established.

Particularly significant, therefore, are the experiments of Comroe & Schmidt (96) demonstrating distinct and often powerful reflex hyperpnea elicited either by active or by passive movements of the limbs. That the hyperpnea was in fact a locally initiated reflex phenomenon and not due to chemical agents liberated into the blood from the active muscles was shown (in man and dog, but not in the cat) by the findings (*a*) that it was not abolished by obstructing the circulation of the limb, and (*b*) that it was absent or became markedly reduced after interruption of the nerve supply. The hyperpnea appeared promptly upon movement and was of significant proportions (e.g., up to 50 to 60 per cent increase in breathing during passive movements of one leg in man) even though only a part of the musculature was involved. The results thus confirm fully the earlier findings of Harrison and coworkers (97). Comroe & Schmidt, while affirming that these reflexes play a part in the hyperpnea of exercise, feel that they fall short of the requirements of a complete explanation in several respects, among them that there is no provision for adjustment of pulmonary ventilation to work done.

The conclusions of Barman, Moreira & Consolazio (98) are at variance with those of Harrison *et al.* and of Comroe & Schmidt. During light exercise of the forearms, in their experiments, and during moderate exercise of the legs (walking), circulatory obstruction in the exercising parts led to a diminished hyperpnea. Release of the obstruction while exercise continued led at once to a marked increase in the hyperpnea above the pre-occlusion level. The authors concluded that "the stimulus to ventilation . . . must therefore be chiefly of chemical, not reflex, origin." It should be remarked, however, that in the experiments of Barman *et al.* the hyperpnea did not disappear during the vascular occlusion. (In a typical example, the minute volume of breathing while walking decreased from 43.7 liters before to 36.9 liters during occlusion.) The reason may have been simply that there was not time for recovery to occur during the short period of the occlusion. It is equally possible, on the other hand, that the marked residual hyperpnea during vascular occlusion was actually due to reflex stimulation of breathing of the type demonstrated by Harrison *et al.* and by Comroe & Schmidt. Thus, while chemical stimulation was shown to be operative during exercise, it is not clear upon what grounds the authors concluded that their experiments exclude the reflex factor.

The importance of nonchemical factors such as this and irradiation of impulses from the motor cortex as postulated by Krogh & Lindhard (99) lies in their potential ability to provide a complete explanation of the hyperpnea of exercise when considered in conjunction with known chemical factors in respiratory control. Such an explanation becomes possible provided two points are recognized: (a) that reflexogenic drive can build upon centrogenic drive and their effects be summed, as shown by Gesell (1), and (b) that the intensity of the centrogenic component may vary in either direction from the base value characteristic of normal resting breathing.

Considering the hyperpnea of moderate exercise below "crest load" because it is this which has presented the greatest difficulties in explanation, it may be assumed that reflex stimulation from the active parts of the body will begin concurrently with the exercise and that this drive, added to the eupneic chemical drive, will result in immediate increase in breathing. After the circulatory adjustments which result in a "steady state" of oxygen consumption

have been consummated, if (as in "static exercise") carbon dioxide is not being eliminated as rapidly as it is formed and delivered at the lungs, then arterial $p\text{CO}_2$ will automatically increase (and so also that of respiratory center and chemoreceptors) until breathing has been sufficiently stimulated to bring about such an equilibrium. In this instance alveolar and arterial carbon dioxide tensions will be above eupneic values when dynamic equilibrium occurs. If, however, as may be the case in "dynamic exercise" the hyperpnea resulting from combined reflex and central drives is sufficiently intense to blow off carbon dioxide from the lungs more rapidly than it is delivered there, then the $p\text{CO}_2$ of arterial blood (and so also of respiratory center and chemoreceptors) will diminish progressively until the resulting loss of chemical drive has reduced breathing to a level at which equilibrium can occur. Concurrently with the hyperpnea, in this instance, alveolar $p\text{CO}_2$, arterial $p\text{CO}_2$, arterial cH , and presumably the cH of the center will all be below eupneic values when dynamic equilibrium finally occurs. When viewed thus the combination of hyperpnea and reduced chemical stimulus, a cause for much concern in the past, becomes an expected phenomenon in the natural course of events. It should be noted that, in each instance, the ultimate controlling factor was variation in central chemical drive, strategically placed at the point of convergence of all other respiratory drives. It should also be noted that for any given type of work, regardless of intensity or of individual variations in the relative values of components, breathing will be proportional to oxygen requirement so long as the respiratory quotient remains constant after "steady state" has been reached and so long as the exercise is below crest load. Beyond crest load, the liberation of carbon dioxide in excess of that resulting from oxidative metabolism would cause breathing to increase out of proportion to oxygen intake, and this is in good agreement with observed behavior.

A number of facts, gleaned from the literature, are in accord with this interpretation of the relationship between proprioceptive reflex and central chemical drives during exercise hyperpnea. For example, on this basis it might be expected that, during the initial stages of vigorous dynamic exercise before "steady state" had been reached, the combined drives acting in advance of actual need (i.e., before cardiac output and pulmonary circulation had reached their maximum) might temporarily overventilate the lungs

and so lead to pronounced lowering of alveolar and arterial carbon dioxide tensions and so also to a secondary period of diminished breathing before equilibrium finally occurred. That this combination of events (initial pronounced lowering of alveolar carbon dioxide tension followed by a temporary recession of hyperpnea) does in fact occur is shown with great clarity in the published records of Benzinger (100). The graphs of Krogh & Lindhard (99) also show the latter phenomenon and, significantly, there appears to be a rough correlation between its occurrence and the vigor of exercise. The latter correlation is also evident in many of the graphs published by Nielsen (27).

That the factor of subeupneic central chemical drive may be a sufficiently powerful negative influence to counterbalance, and so control, powerful reflex drive is indicated by the further experiments of Krogh & Lindhard (99). Subjects beginning an exercise which would normally have been accompanied by immediate intense hyperpnea remained apneic for several seconds following its onset when it had been preceded by forced breathing. Inhalation of 3 per cent carbon dioxide, on the other hand, markedly intensified the initial hyperpnea of exercise.

The scope of this review does not allow further discussion of the hypothetical explanation of exercise hyperpnea made possible by recent developments. It may be noted in conclusion, however, that this concept of respiratory regulation during exercise substitutes increased excitation at the center (summation of drives) for an hypothetically increased central excitability to a single stimulus (carbon dioxide) as has been postulated by Krogh & Lindhard (99), Nielsen (27), Henderson (101), and others.

THE EFFECTS OF NARCOTICS AND ANESTHETICS UPON THE BALANCE OF COMPONENTS IN RESPIRATORY CONTROL

The degree to which anesthetics and narcotics might distort normal interrelationships among the components of the respiratory control mechanism has long been an imponderable which has required that interpretations of experimental results be tentative and which has created confusion and uncertainty in the practical application of principles of respiratory control on the part of the anesthetist. The work of Marshall & Rosenfeld (75) uncovered basic principles in this connection and some of the observations of Comroe & Schmidt (88) led them to essentially similar conclusions.

This earlier work has gone unheeded for too long and the current rise of interest in this phase of respiratory physiology, which has already led to confirmation and emphasis and some amplification of Marshall & Rosenfeld's conclusions, promises a sounder and more rational experimental approach to the complex problems of respiratory control.

In the experiments of Marshall & Rosenfeld it was shown (*a*) that under the influence of certain anesthetics the respiratory response to carbon dioxide was diminished to the point of disappearance; (*b*) that under these conditions the maintenance of breathing became increasingly, and finally almost completely, dependent upon an anoxemic stimulus, the latter acting mainly if not entirely through the sino-aortic (chemoreflex) mechanism; and (*c*) that, because of (*a*) and (*b*), oxygen administration caused apnea and might lead to respiratory failure. Among the anesthetics studied, barbiturates and barbiturates plus morphine produced these effects most markedly. The effects were less in evidence when chlorbutanol urethane, paraldehyde, and alcohol were used. The determining factor appeared to be the relative balance between anoxemia on the one hand and other extrinsic or intrinsic factors in maintaining respiration on the other.

Schmidt (102), discussing preliminary data from his laboratory, added another point which has played a potent part in the interpretation of experimental results, especially those concerned with the chemoreflex control of breathing. This added point was that certain anesthetic agents, notably chloralose and morphine, contributed to the unbalance of factors such as that described by Marshall & Rosenfeld, not only by causing a relative increase in chemoreflex influence through depression of central response to carbon dioxide, but also by actually exaggerating chemoreflex excitability. This point will be mentioned again later.

Recently, in a series of carefully performed experiments (103, 104) Moyer & Beecher have completely confirmed the conclusions of Marshall & Rosenfeld so far as barbiturates are concerned (sodium evipal, pentothal) and they (104) have traced the changes in balance between central and chemoreflex components of respiratory control through several depths of anesthesia.¹⁰ Numerous

¹⁰ The effects of anesthetics upon the Hering-Breuer reflexes were reported also by Moyer & Beecher (105), Moyer (106), and by Moyer & Beecher (107).

applications of these findings to the management of anesthesia under both clinical and experimental conditions were made. One rather surprising finding, in view of generally held ideas concerning the relative diffusibilities of oxygen and carbon dioxide, was that the minute volume of respiration necessary for the maintenance of normal arterial oxygen content of some anesthetized animals was less than that necessary to effect removal of carbon dioxide.

A point upon which the experiments of Moyer & Beecher differed from others was the finding of actual depression of breathing by carbon dioxide under very deep anesthesia. Lest this lead to further confusion, we think it should be noted that the carbon dioxide mixtures inhaled also contained an increased percentage of oxygen (28 per cent) and that the reaction noted may have been the oxygen depression of Marshall & Rosenfeld rather than an effect of carbon dioxide. This interpretation is supported by the observation that, in all of the animals in which depression occurred, the minute volume of breathing and the oxygen content of the arterial blood had been lowered excessively under the influence of the anesthetic. (In the experiments of Dripps & Dumke, to be described below, it is likewise probable that the depression of the central response to carbon dioxide was exaggerated since the carbon dioxide was administered in 90 per cent oxygen.)

In the experiments of Dripps & Dumke (90), the effect of narcotics on the balance between central and chemoreceptor control of breathing was studied by comparing data for minute volume of breathing, minimum effective dose of cyanide (chemoreflex excitability), and respiratory response to carbon dioxide inhalation (central excitability to chemical stimulation) at progressively intensified degrees of anesthesia in decerebrate dogs and cats. Chloralose, morphine, ether, and cyclopropane were studied in addition to barbiturates. An effect common to all of these agents was their depression of the response of the respiratory center to increased carbon dioxide. The results were in general agreement with those of Marshall & Rosenfeld and of Moyer & Beecher but brought out some further points. One of these was the peculiar effects of ether which decreased both the response to carbon dioxide and the chemoreflex response and yet increased the minute volume of breathing. Another concerned chemoreflex excitability and merits special attention because of its bearing upon the interpretation of ex-

perimental results derived from anesthetized animals. The response to cyanide was increased under the influence of all of the anesthetics used except ether and cyclopropane. However, in all of these instances minute volume of breathing was diminished and, in cases in which determinations were made, the arterial oxygen tension likewise had been lowered. The possibility was therefore considered that the responses to cyanide were increased not because of actually increased reflex excitability but simply because of added hypoxic stimulus resulting from the diminished pulmonary ventilation. In other words, increased excitation rather than increased excitability of the chemoreflex mechanism may have been induced. This conclusion was borne out by control experiments in which it was demonstrated that removal of anoxemia by oxygen inhalation restored chemoreflex sensitivity to cyanide approximately to normal and that the response to a constant dosage of cyanide could be varied several hundred per cent by varying the percentage of oxygen in the inspired air.

MISCELLANEOUS TOPICS

Aspects of anoxia.—Horvath, Dill & Corwin (108) find that human patients subjected to severe anoxia over a period of several minutes and extending into unconsciousness experience no lasting harmful effects on the central nervous system, exhibit strong and sustained respiratory stimulation and recover rapidly when air or 14 per cent oxygen is administered. They conclude that it should be possible to descend with an opened parachute from 31,000 feet altitude without oxygen equipment and with no ill effects from anoxia.

The advantages and disadvantages of carbon dioxide inhalation at high altitudes continue to be discussed. Johnson, Eckman, Rumsey & Barach (109) found the arterial oxygen saturation of dogs breathing oxygen at simulated altitudes of 35,000 to 38,000 feet unchanged by addition of carbon dioxide to inspired air. The oxygen saturation of mixed venous blood fell progressively regardless of whether oxygen or an oxygen-carbon dioxide mixture was inspired. They conclude that, despite an increase of minute volume of breathing, the lack of beneficial effects of carbon dioxide inhalation on the oxygen tension of mixed venous blood precludes its use in human subjects without special indications. It might be held that this point of view overlooks the possible beneficial ef-

fects of redistribution of blood flow in favor of the brain under the influence of raised carbon dioxide tension and facilitated liberation of oxygen from oxyhemoglobin. However, Himwich, Fazekas, Herrlich, Johnson & Barach (110), continuing these studies, reported no significant change in the oxygen and carbon dioxide content of venous cerebral blood when 10 per cent carbon dioxide was inhaled.

Stickney & Van Liere (111), studying the effects of discontinuous exposure to anoxia upon acclimatization, find that $6\frac{1}{2}$ to 9 hours a day spent at simulated altitudes of 12,000 to 18,000 feet produced a noticeable increase in erythrocytes and hemoglobin values, the degree being proportional to the severity of anoxia and the length of exposure.

Dorrance, Thorn, Clinton, Edmonds, & Farber (112) confirmed earlier findings of others that cobaltous ion in small doses induced polycythemia. Rats so treated exhibited increased work performance under conditions of hypoxia.

Darling & Roughton (113) have reported their discovery that in methemoglobinemia the dissociation curve of the ordinary hemoglobin is shifted to the left and becomes less sigmoid and more hyperbolic, the effect being similar to that produced by carbon monoxide-hemoglobin. Accordingly in methemoglobinemia the tissues are liable to anoxemia not only from loss of oxygen capacity of the blood, but also from difficulty in unloading from the blood such oxygen as may be present.

Warren, Peterson & Drinker (114) have described the anatomy of the lung lymph drainage in the dog and the effects of heightened negative intrathoracic pressure and of anoxia upon the flow of lung lymph. A sudden increase of lung lymph flow resulted from the use of a 10 per cent oxygen mixture for artificial ventilation. This effect was shown to be the result of abnormal permeability of the lung capillaries due to the hypoxia. Recovery was prompt following reinstatement of an adequate oxygen supply.

Exposure to oxygen at high barometric pressures induces residual dysfunction, chiefly neuromuscular, which may persist for as long as ten weeks in the rat, according to Bean & Siegfried (115) who suggested that an irreversible change in enzymatic cellular processes may be responsible.

In experiments directed toward the evaluation of certain meth-

ods of artificial ventilation in man, Hooker, Kouwenhoven & York (116) found the Pole-top method in the trunk vertical position more efficacious than the Schaeffer method in the prone position, and the modified Schaeffer method superior to the original Schaeffer method. More air is moved in the unconscious than in the conscious subject by any of these methods.

Franseen & Hellebrandt (117) continuing their study of postural metabolism in human subjects, found that respiratory changes occurring as verticality was approached outstripped concomitant increases in metabolism and attributed this result to interference with blood flow to the head.

Studies contributing to the comparative physiology of respiration have dealt with respiration of the armadillo (118), vagus action in birds (119), and the effects of variations in the composition of the inspired air upon the respiration of reptiles (120). Powers & Clark (121) reported experiments which led them to conclude that the control of breathing in fishes is predominantly chemoreflex, the receptors being located in the gill region and innervated by the ninth cranial nerves.

Hammouda, Samaan & Wilson (122), investigating the origin of the reflex respiratory effects of inflation or deflation of the lungs, concluded that these effects originated entirely in intrapulmonary nerve endings and not from extrapulmonary sources such as thoracic wall or diaphragm. They concluded further that both the respiratory accelerator fibers and the respiratory inhibitory fibers of the vagus nerve trunk are of intrapulmonary and not of cardiac origin.

Nicholson & Trimby (123) have described a new method for recording respiration by continuous determinations of the buoyancy of an animal submerged in water. The advantage of the method over spirometer tracings lies in the fact that changes in level of the tracing are due solely to changes in chest volume associated with changes of tonus of respiratory muscles and are not complicated by variations in oxygen consumption of the animal. Application of the method to study of vagus function revealed a predominantly expiratory augmenting action in accordance with Gesell's concept of the vagus as an excitatory rather than an inhibitory nerve. A vagal inspiratory augmenting influence was also demonstrated. The method was applied to the study of interrelationships between inspiratory and expiratory activity under a variety of experimental conditions.

Other innovations of methods are represented by the acoustic respirograph (124) with which breathing may be studied by graphic recording of breath sounds and by the electrostethograph (125) which applies the cathode ray oscillograph to the visualization of breath sounds.

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THE PHYSIOLOGY OF THE SKIN

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This review covers the literature of the period from July 1941 to September 1943. Studies on effects of heat and cold, on the participation of the skin in heat regulation, and on radiation effects are not included because they are covered in other chapters. Studies on cutaneous sensory perceptions are discussed only insofar as they are related to itching sensation; pain, touch, and temperature senses are reviewed elsewhere in this volume. Those publications which deal with rather specific physiological functions of the skin, such as keratinization, pigment formation, and formation of long chain fatty acids and alcohols by the sebaceous glands are emphasized. The reviewers apologize for referring to pathological conditions perhaps too often. However, the interrelations of physiology and pathology have brought particularly fruitful results in the experimental work on the functions of the skin. While selecting the material the reviewers noticed with great regret the absence from research in their field of many excellent investigators who in earlier years greatly contributed to the scientific foundation of dermatology, but who now are fully devoted to their practical work in the war effort.

Nutritional factors.—Observations of nutritional deficiencies produced experimentally in mammals and birds have made it obvious that for the maintenance of normal functions of the tegument a diet is required which is not deficient in vitamins. In most of the experimental deficiencies, severe cutaneous disorders are conspicuous and early signs of the deficiency syndrome. With a few exceptions, however, these cutaneous disorders are not characteristic enough to allow us to draw conclusions on the influence of single vitamins on single physiological functions. Clinical experience has taught that responses of the skin to widely varying stimuli may be identical, and specific responses cannot always be expected. In addition, a complicating factor arises from the interrelationship of vitamins. This circumstance may cause with-

drawal of a single factor to lead to disturbances in the utilization of others.

The presence of vitamin A is necessary for the maintenance of a normal keratinization of the surface epidermis and of the follicular epithelium. Frazier & Hu reported as early as 1931 observations on vitamin A-deficient individuals in China who displayed the signs of keratosis pilaris, a hyperproduction of keratin material in the follicular orifices; this cutaneous disorder was cured by the administration of vitamin A. Recently the role of vitamin A in the maintenance of normal keratinization was demonstrated in rats by Moulton (1). In these experiments, vitamin-A deficiency led to a condition very similar to that observed in human beings. Initially there was a slight general hyperkeratosis, which was followed by increased keratinization of the follicular epithelium. Later the follicles became distended and plugged with keratin material. In the final stages, cessation of hair growth, atrophy of the sebaceous glands, and complete disorganization of the hair follicles were seen. The atrophic process was due to the mechanical obstruction of the follicle by horny masses.

The response of the follicular epithelium to the withdrawal of vitamin A in man depends on the developmental stage of the pilosebaceous apparatus; it is less pronounced in infants and in children before adolescence than in adults (2).

Attempts were made to use vitamin A therapeutically in several pathological conditions which are associated with follicular hyperkeratosis (3 to 7). The therapeutic results in Darier's follicular dyskeratosis, as first observed by Peck, are particularly puzzling because, in the majority of cases, no definite signs of vitamin-A deficiency could be found in this hereditary condition (8, 9). The influence of vitamin A on keratinization is the more mysterious as no vitamin A is present in measurable quantities in normal epidermis (10).

Several B factors, such as biotin, pyridoxine, pantothenic acid, and riboflavin are necessary for the maintenance of normal cellular functions in the mammalian skin. In their absence disturbances of the cell life develop which lead to inflammatory reactions in the form of oozing and scaling dermatitis. The symptomatology of these deficiencies and their possible relations to human pathology were discussed by Gyorgy in 1941 (11).

The cutaneous signs of biotin deficiency ("egg-white injury") in rats were studied by several authors (12 to 15). The outstanding

sign is a generalized erythematous pruritic dermatitis with greasy scaling. The inflammation is followed by sloughing of the stratum corneum and by epidermal atrophy; furthermore, follicular keratosis was found microscopically. Biotin is an essential dietary factor also in chicks (16, 17) and in turkeys (18).

In human beings an experimental study was conducted with four volunteers; the biotin deficiency was produced by the administration of large amounts of egg white during several weeks. After three to four weeks on this diet, these individuals developed a fine scaling of the skin. The scaling was obviously due to a mild chronic inflammatory process as proved by the appearance of a maculosquamous dermatitis in one of the subjects (19).

Rats deficient in pyridoxine show a dermatitis with congestion, edema, hyperkeratosis, acanthosis, and later necrosis on the paws, snout, and ears (20, 21, 22). This condition has been called "rat acrodynia." Similar cutaneous disturbances were produced by a diet poor in unsaturated fatty acids and could be cured by administration of ethyl linolate. In this fatty acid deficiency pyridoxine caused temporary alleviation but did not effect a cure. Amounts of linolate which were subcurative alone became curative when given with pyridoxine. The addition of pantothenic acid to the diet supported the curative effect of linolate and pyridoxine. However, the mechanism of the interrelation of these three substances has not been clarified (23, 24). In a short note Williamson (25) reported on thickening of the epidermis with hyperkeratosis and particular differentiation of the granular layer in rats kept on a fat-free diet. A fat-free diet supplemented with unsaturated fatty acids did not effect such changes.

It has been claimed that persons affected with oleic seborrhea and acne vulgaris respond favorably to the administration of pyridoxine (26).

In rats and mice, pantothenic acid deficiency produced by a diet low in this vitamin (27, 28, 29), or by addition of zinc chloride to the diet (30), often is followed by a dermatitis similar to that seen in biotin deficiency. It was assumed (31) that lack of pantothenic acid has only an indirect effect in the production of cutaneous inflammatory deficiency symptoms; in its absence the metabolism of both pyridoxine and fatty acids is disturbed.

A characteristic sign of pantothenic acid deficiency is the so-called blood-caked whiskers, consisting of porphyrin incrustations, the porphyrin originating from the lacrimal glands (32, 33).

It is noteworthy that dermatitis was observed in rats on a synthetic diet, even when it was supplemented by all hitherto known accessory food factors (34). This finding suggests that unknown dietary factors also may participate in the maintenance of normal functions in the skin (34, 23).

In man, riboflavine apparently has a greater role in the maintenance of physiological conditions in mucous membranes and mucocutaneous junctions than it has in that of the skin. In fully developed riboflavine deficiency with cheilosis and linear fissures in the corners of the mouth, the skin displayed but mild greasy scaling on the nasolabial folds (35). The cutaneous signs of riboflavine deficiency in rats also have definite seborrheic qualities (36).

Nicotinic acid deficiency, produced in growing chicks by a diet low in this vitamin, caused inflammatory signs in the entire mouth cavity, in the upper portion of the esophagus, and in the crop. No pigmentation was noted (37). Handler & Dann (38) reexamined the problem of canine blacktongue and found that the changes on the mucous membranes in nicotinic acid deficiency could be counteracted by administration of large amounts of saline. Handler (39) noted that simple withdrawal of nicotinic acid caused milder symptoms than the Goldberger diet, and concluded that the presence of cornmeal *per se* in the diet may be an etiological factor in pellagra. The experiments of Schaefer *et al.* (40) showed rather different results. They fed dogs a synthetic diet containing all B factors except nicotinic acid and, in this way, produced blacktongue like that described by Goldberger.

Moore *et al.* (41) studied the histopathology of human pellagra and found dyskeratosis, atrophy of the epidermis, and inflammation not only in manifest lesions but also in clinically unaffected skin. Aside from this study, no significant contributions were made in the field of human pellagra during the period covered by this review. However, the literature up to 1941 has been considered by Smith (42) in his detailed and critical study which deals with the history and treatment of pellagra.

The effects of vitamins on pigmentation and hair growth are discussed in the following sections.

Pigmentation.—The problem of the mechanism of melanin formation and its influencing factors has been approached both by *in vitro* experiments and by studies on the living animal.

The *in vitro* experiments were based either on the tyrosine-tyrosinase reaction or on the dopa reaction of Bloch. The presence

of the tyrosinase enzyme never has been conclusively demonstrated in the skin of mammals. It has been assumed that the immediate precursor of melanin in mammalian skin is 3,4-dihydroxyphenylalanine (dopa) which is oxidized to melanin in mammalian melanoblasts by a specific intracellular oxidase. The substrate dopa, however, does not occur in animal proteins (43), and so melanogenesis in mammals never has been satisfactorily explained. Rothman (44) showed that, *in vitro*, tyrosine is easily transformed into dopa by mild ultraviolet radiation if small amounts of ferrous salts are present. He concluded that such mechanism may account for the formation of dopa and subsequently of melanin in human skin following exposure to sunshine. In other words, in mammals too, the primary precursor of melanin could be tyrosine, despite the lack of tyrosinase. Thus, although the mechanism is somewhat modified, studies on the tyrosine-tyrosinase system may be contributory to the physiology of pigment formation in mammalian skin.

After clinical observations had been made on the local bleaching effect of the antioxidant hydroquinone monobenzylether ("Agerite alba") on the skin of Negroes, Peck & Sobotka (45) demonstrated that the histologic dopa reaction was inhibited by "Agerite alba," and the oxidation of tyrosine by tyrosinase was stopped by it in the red stage. Baker *et al.* (46), confirming and extending earlier observations of Martin *et al.* (47), found that *p*-aminobenzoic acid, sulfanilamide, *p*-aminoacetanilide and β -naphthylamine interfered with the tyrosine-tyrosinase reaction. Even if these observations were made under nonphysiological conditions, they at least had demonstrated convincingly that *p*-aminobenzoic acid has no direct furthering effect on pigment formation as had been originally assumed. Rather, its direct action, if any, is slightly inhibitory.

In studying the inhibitory effect of ascorbic acid on melanin formation, Rothman (48) found that it furthers the first step of actinic oxidation of tyrosine, namely, the transformation of tyrosine into dopa, but that it completely inhibits any further oxidation. In contrast to ascorbic acid, other reducing agents, such as sulfurous acid and cysteine, were found to inhibit the oxidation from the very beginning, suppressing the formation of dopa from tyrosine.

Figge (49) observed a complete inhibition of the oxidation of tyrosine by tyrosinase in the presence of glutathione. When, how-

ever, estrone was added to such a system in equivalent amounts with glutathione, the inhibitory action of the latter was abolished. One may assume that this action of estrone accounts for the furthering effect of estrogenic substances on pigmentation *in vivo*. Within the cell, estrone may release the oxidase from the inhibitory effect of sulfhydryl groups.

Sharlit *et al.* (50) noted that keeping formalin-fixed frozen sections of the skin in an incubator for a few hours, as is required in the technique of Bloch's dopa reaction, resulted in the formation of new melanin granules. This formation of new pigment was even more intense if the sections were incubated with solutions of sodium fluoride or potassium cyanide, or if the aqueous solutions in which the sections were placed were overlaid with liquid petrolatum and then saturated with oxygen and carbon dioxide. The majority of those who discussed the paper of Sharlit *et al.* expressed the opinion that the described phenomena might be explained by the appearance of the dark oxidized form of melanin granules. Earlier, it had been shown (51) that the so-called postmortal pigmentation as elicited by heat, by long-wave ultraviolet irradiation, or by treatment with silver nitrate does not represent formation of new melanin but is the result of an oxidation of the hardly visible pale "reduced melanin" into the darker oxidized form. In Sharlit's experiments the combination of the effects of heat and chemicals might have been interpreted on the basis of a similar mechanism.

Rothman (48) observed that by reducing melanin with ascorbic acid, light brown to yellow water-soluble products were formed. Following clinical experiments, he concluded that the bleaching effect of large amounts of ascorbic acid given perorally in Addison's disease is due to this reducing action rather than to a prevention of formation of new melanin.

Vigorous oxidation of melanin also leads to its decomposition yielding water-soluble pale products. Such decomposition is in a dynamic equilibrium with formation of new melanin in individuals who are already tanned to a maximum and are further exposed to ultraviolet radiation (52).

The first evidence for a different mechanism of red pigment formation, in contrast to the formation of the brown-black melanin pigment, was presented by Rothman & Flesch (53) by the isolation of a new type of pigment from human red hair. In their preliminary report, they described this substance as a complex phenolic iron

compound, soluble in strong acids with a brilliant red color, and changing to brown reversibly at pH 2.5. The substance is precipitated at the neutral point and again goes into solution at above pH 7 with a brown color. In contrast to the hitherto described cutaneous pigments of mammals, it has a characteristic absorption spectrum with a band having a maximum at 535 $m\mu$ in acid solution. Obviously the compound is not a porphyrin or porphyrin derivative. The data presented by the authors indicate that its phenolic hydroxyl groups are attached to a heterocyclic ring containing nitrogen. This iron pigment was found only in bright red human hair; the redder the hair, the greater the yield. Yet the iron pigment seemed to contribute little to the red color of the hair; after its complete extraction the hair still appeared red. Nevertheless, its invariable presence in red hair indicates that it must have a role in the pigmentation of red-haired persons.

During the period covered by this review two main groups of factors influencing skin pigmentation in living animals were studied: (a) hormones which were known for a long time to have an effect on the color of the skin and hair, and (b) nutritional factors, the study of which constitutes a recent chapter in the physiology of pigmentation.

The well known furthering effect of estrogenic hormones on the pigmentation of both male and female animals was studied in detail by Forbes (54). He implanted pellets of different estrogenic substances subcutaneously into male and female rats and found that their fur darkened after this treatment. A similar effect was observed after the implantation of androsterone but not of testosterone. An unusual observation by the same author was that of estrogenic hyperpigmentation in albino animals; this observation is inconsistent with all earlier data which indicate that only functioning melanoblasts, not present in albinos, respond to any kind of pigmentogenic stimuli.

In the young castrated male guinea pig unilateral pigmentation of the areola mammae was observed after external application of stilbestrol to one nipple (55). This finding indicates that estrogenic substances act directly (not through the circulating blood or the nervous system) on the melanoblasts of the areola. The local action within the cell, however, may not be direct but indirect by binding sulfhydryl groups which, when free, inhibit pigmentation (49). It was found (55) in castrated male guinea pigs that injections of stilbestrol cause hyperpigmentation not only on the areolae and

in the linea alba but also on the skin of the scrotum. The estrogenic hyperpigmentation was completely inhibited by the simultaneous administration of chorionic gonadotropic hormone.

Much attention has been paid to the physiological role of the adrenal glands in pigmentation. Until recently the hyperpigmentation in adrenal insufficiency, as seen in Addison's disease, could not be reproduced in animal experiments. Butcher was the first to succeed in demonstrating hyperpigmentation in animals after adrenalectomy. His experiments were confirmed and extended by Ralli & Graef (56) who worked on rats, one group of which was kept on a diet deficient in the filtrate factor. This group showed marked graying of the fur if kept long enough on this diet. In the germinative cells of the follicles of the gray hairs the dopa reaction was negative. In these deficient grayed animals bilateral adrenalectomy caused return of melanin deposits; in fact, they became darker than they had been before the initiation of the deficient diet. The dopa reaction in the follicular epithelium became positive simultaneously with the visible darkening of the fur. The control group of rats being kept on a normal diet showed, after adrenalectomy, a similar increase in melanin formation. Increased pigmentation after adrenalectomy was strictly confined to skin areas containing functioning melanoblasts. White rats did not display any change in the color of the fur.

The role of single B factors in the maintenance of normal pigmentation of skin and hair is still not entirely clarified. The observation that a diet deficient in pantothenic acid alone leads to graying of the hair ("achromotrichia") in rats, mice, dogs, and chicks, and that this condition can be reversed by the addition of pantothenic acid to the diet has been amply confirmed (28, 29, 30, 57 to 60). More recent findings, however, indicating that *p*-amino-benzoic acid plays a similar primary role in the maintenance of the color of the fur in rats and mice (61), were challenged by several authors (28, 57, 58). Graying of the fur was also observed in animals deficient in either biotin (12, 15) or folic acid (62). Several theories were advanced to account for these discrepancies (62, 63). Wright & Welch (64) suggested a working hypothesis which agrees with all hitherto established facts. The authors assume that the primary chromotrichia factor among the members of the B complex is pantothenic acid. According to the theory, in the absence of folic acid or of biotin, pantothenic acid cannot be synthesized because of an inadequate intestinal flora, or the tissues cannot

utilize it. The role of *p*-aminobenzoic acid, then, is to stimulate bacterial growth and thereby the intestinal synthesis of folic acid which, in turn, improves the utilization of pantothenic acid.

A remarkable sex difference concerning graying of the fur in pantothenic acid deficiency was reported by Gerstl *et al.* (65), who found that on the thirtieth day of the experiment graying of the fur occurred in 55 per cent of male mice and in only 6 per cent of the female.

The observations on nutritional achromotrichia in rodents led to attempts to restore the hair color in gray-haired human beings by the administration of different vitamin B factors. Most of these studies lack the fundamental requirements of scientific experimentation, and it is highly regrettable that exaggerated claims were raised and commercially exploited in this field. Complete failure in restoring the original hair color in canities by administration of large doses of pantothenic acid and of *p*-aminobenzoic acid was reported by several authors (66, 67). In especially well controlled experiments Brandaleone *et al.* (68) administered pantothenic acid, *p*-aminobenzoic acid, and yeast in various combinations to a group of nineteen elderly individuals with graying hair. In seventeen cases, there were no changes at all, or else the hair assumed a yellow or greenish cast, possibly the result of excretion of decomposition products of *p*-aminobenzoic acid through the follicles. Only in two individuals was there a change of hair color which might be interpreted as some degree of return to the original shade. These two individuals received both pantothenic acid and *p*-aminobenzoic acid, together with yeast.

Reports on a remarkable spreading tendency of pigmentary functions in skin grafts were published almost simultaneously, but independently, by Lewin & Peck in New York (69) and by Fessler in London (70). In both series of experiments, white and dark skin grafts taken from spotted guinea pigs were interchanged by transplantation. Whereas white transplants darkened by taking up the color of the surrounding host skin, transplanted pigmented grafts induced pigmentation to the surrounding unpigmented skin. Extension of pigmentation was observed as early as three weeks after transplantation, and there was a continuous centrifugal spread of pigmentation into the white surroundings over a period of two years (70). Fessler emphasized that this phenomenon is a sign of higher vitality in melanoblasts as compared with nonpigmentary epidermal cells.

Hair growth.—Studies on hair growth, like those on pigment formation, deal mainly with the influence of hormonal and nutritional factors.

Butcher (71) working on underfed albino rats established the fact that adrenalectomy considerably accelerates hair growth in such animals. He showed that this effect cannot be attributed to an indirect influence of the thyroid gland. The accelerated hair growth is preceded by an increase in the oxygen consumption of the skin (72). Ralli & Graef (56), who worked with black and brown rats that were kept on a diet deficient in the filtrate factor, confirmed Butcher's findings. They observed that this diet caused atrophy of the hair bulbs and follicles and that this progressive atrophy could be overcome by adrenalectomy. Moreover, these authors noted a similar stimulating effect of adrenalectomy on hair growth in healthy animals kept on a normal diet.

In disagreement with these findings is the work of Stein & Wertheimer (73). In their experiments, adrenalectomy in otherwise normal rats was followed by an increased loss of hair. The authors substantiated this observation by weighing the amounts of shed hair in operated, in normal, and in sham-operated animals. Rats in which the adrenal medulla alone was removed also showed a transient increase in hair loss. According to the authors, this effect could be checked by subcutaneous injections of epinephrine, but not by the administration of cortical or sex hormone preparations, with vitamins, cystine, or both.

If large amounts of estrogens are administered to rats whose hair has been clipped, no regrowth occurs. These earlier observations were confirmed by Hooker & Pfeiffer (74). After two months' treatment of animals kept on a basic diet and given 83 μ g. of estradiol benzoate twice weekly, the coats became shaggy with a thinning of the hair and with the appearance of areas almost denuded of hair. Regrowth of hair in shaved areas required approximately three times as long as regrowth in similar shaved areas of untreated rats. In addition to follicular atrophy, all layers of the skin were found to become atrophic. The number of sebaceous glands decreased strikingly, and the individual sebaceous glands were not more than one-fifth as large as in the untreated animals, sometimes consisting of but three or four cells. In Hooker & Pfeiffer's experiments all these cutaneous effects of estrogens were completely counteracted when androgens (2.5 mg. of testosterone

propionate twice weekly) were administered simultaneously with the estrogens.

The old clinical experience that eunuchoids and male castrates do not develop premature alopecia was confirmed by Hamilton (75). He succeeded in inducing typical early baldness of the male type in such individuals by administration of androgenic hormones. In his patients, the alopecia progressed as long as the treatment was continued; cessation of therapy prevented further enlargement of bald areas but did not promote regrowth of hair. This effect of androgenic hormone, however, was observed only in those eunuchoids and castrates whose families tended to become bald. The author concluded that both the hereditary factor and the presence of male sex hormones are obligate prerequisites of early male baldness. The complexity of the problem of this condition was discussed extensively by Rattner (76).

After earlier observations had indicated that inositol ("mouse alopecia factor") was essential for the maintenance of normal fur in mice, other B factors were found to be of importance for the normal growth of hair. As is the case with "chromotrichia factors," the action mechanism and interrelationship of the members of the B complex causing alopecia are poorly understood.

Diffuse and circumscribed forms of alopecia (including circumocular alopecia, called "spectacled eyes") were reported in riboflavine (36), biotin (12, 15, 77, 78), pantothenic acid (29, 30, 79), fatty acid (23), and pyridoxine (22) deficiencies. Microscopically, first dilatation of the follicles, then plugging of the orifices with horny material and finally atrophy (possibly pressure atrophy) are seen. Hair growth can be restored by supplementation of the lacking vitamin in follicles which are not yet atrophic. The treatment of human baldness with inositol was without any beneficial effect (67).

Keratinization process.—One of the most characteristic biologic processes in the skin is the continuous formation of keratin in the horny layer, in hair, and in nails from epithelial cell proteins. The chemical and physical nature of this process has been previously clarified by the work of Astbury, Michaelis, and others. X-ray spectrograms have shown that the coiled polypeptide chains of cell proteins are straightened when transformation to keratin takes place. The high resistance of horny material to hydrolytic agents, enzymes, and chemicals, is due to formation of cystine-

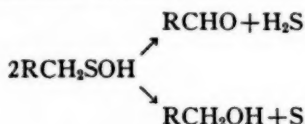
bridges ($-S-S-$) and salt linkages between the straight polypeptide chains.

Recently Huggins (80) reviewed the structure of α - and β -keratin and of other "fibrous proteins." He particularly favors the assumption that in these proteins the attraction between carbonyl groups and imino groups of neighboring polypeptide chains leads to the formation of $-N \cdots H-O-C-$ bridges between the chains. He states that his crystallographic formulas are in better agreement with the available x-ray spectrographic data than the structures hitherto suggested.

In a series of publications Stoves (81, 82, 83) described the effect of alkalis, and of reducing and oxidizing agents on the cystine linkage of the keratin of human hair. His work was based on measurements of tensile strength by means of a balance-type extensometer. The changes in tensile strength of the alkali treated hair under the influence of different reagents permitted conclusions on the chemical nature of the decomposition process. Stoves stated that the first reaction to occur in alkali treated keratin fibers is hydrolysis of the cystine linkages to form sulfenic acids:

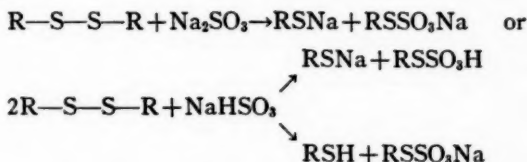


The sulfenic acids break down to give rise to aldehydo acids and to alcohols by elimination of sulfur:



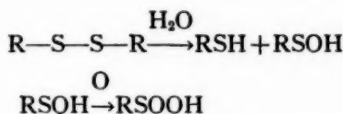
These secondary compounds react with the other polypeptide chains of the fiber to form new $-N=CH-$ and $-C-S-C-$ bridges between the chains. The existence of these new types of linkages was proved by their resistance to sodium metabisulfite. The formation of the $-CH=N-$ bonds was prevented by the addition of methylamine; treatment of the hair with alkalis and methylamine together caused a rapid disintegration of hair. The final values of tensile strength obtained after the treatment of keratin fibers with alkalis depends upon the extent to which these various reactions have taken place. This, in turn, depends on the time of treatment together with the temperature, concentration, and pH of the solution used.

Reducing agents split the —S—S— bond by the following reactions:



In contrast to the effect of alkaline treatment of the hair, reducing agents do not lead to the synthesis of new bonds. When the extent of cystine linkage breakdown was not excessive, loss of tensile strength of bisulfite treated fibers could be completely restored by subsequent treatment with aqueous solutions of benzoquinone, formaldehyde, potassium bichromate, or of salts of divalent metals.

Oxidizing agents first hydrolyzed the cystine linkage and then oxidized it:



The degree of cleavage depends upon the pH, temperature, concentration of the oxidizing agent, and the presence of copper, nickel, cobalt, or iron salts, acting as catalysts. Stoves was able to restore the tensile strength of fibers damaged through oxidation by subsequent treatment with benzoquinone or formaldehyde. The rebuilding of linkages, however, was less complete than in the fibers treated with reducing agents. Mercuric acetate in 0.1 *N* acetic acid increased the strength of oxidized fibers considerably beyond that of normal hair.

In a more recent publication Stoves (84) reported on the different chemical behavior of the cortical and medullary portion of the guard hair in Russian hares. Histochemical reactions showed that the medulla contains more tyrosine and the cortex is richer in cystine.

Chiego & Silver (85) studied the effect of alkalies on human hair and nails. They found that the cystine linkages of these horny substances are easily split by alkalies above pH 9.2. Clinical studies led the authors to the conclusion that, in the causation of

brittleness of the nails, hydrolysis by alkalies following the excessive use of strong soaps is a primary factor.

Lipid secretion.—A valuable contribution to our knowledge of the lipid metabolism of the skin organ was made by Burtenshaw (86) when he examined the mechanism of the disinfectant action of the skin and its appendages. He found that the bactericidal effect of horny layer scrapings, hair, nails, and cerumen on hemolytic streptococci is due to the ether-soluble fraction of these materials. Burtenshaw made a detailed analysis of the fatty substances occurring in the skin and its appendages. His analytical values seem to support the older conception that lipids from skin regions without sebaceous glands consist of oleic and other unsaturated fatty acids with their esters and soaps, of cholesterol and its esters, and of traces of the short chain fatty acids; whereas fat from skin supplied with sebaceous glands, fat from hair and from cerumen contains numerous long and short chain fatty acids with their esters and soaps but no cholesterol. Burtenshaw's data suggest that the hair fat is a mixture of sebum and sweat lipids together with a small contribution of epidermal cholesterol.

Burtenshaw tested the bactericidal power of different fractions from various suspensions and extracts of horny materials. He found that these materials were bactericidal owing to their content of oleic acid, of other long chain fatty acids, and of their soaps. The esters of these acids, the sterols, higher alcohols, and short chain fatty acids, including lactic, citric, and ascorbic acids and their sodium salts were inactive. The long chain fatty acids were far more bactericidal at an acid reaction than at an alkaline reaction. Increased concentration of hydrogen ions acted not only by their own toxicity on bacteria but also by the release of the highly bactericidal fatty acids from their less active soaps. Unsaturated long chain fatty acids showed high antiseptic power, but this power was not always dependent on the degree of unsaturation. Apparently the disinfectant ability of single compounds depends upon several factors, mainly on the lowering of the surface tension, on water solubility, and on the molecular constitution (long chains with hydroxyl, amino, and carboxyl groups). Burtenshaw found that cysteine inhibited the streptococcicidal activity of skin fats, and that this inhibition could not be explained solely by the reducing action of cysteine on peroxides. Blood, an oxidizing agent, was found to be even more effective than cysteine

in diminishing the streptococcocidal power of fatty acids. On the other hand, ultraviolet rays in some cases counteracted the inhibition exercised by cysteine, possibly by oxidative mechanisms.

The original paper of Melczer & Deme (87) dealing with the microchemistry and histochemistry of sebaceous gland secretion was not available to the reviewers. According to the available abstract, the authors reported on three layers of lipids in the lumen of the sebaceous glands. The outer layer was composed of fatty acids, the middle zone of long chain aliphatic alcohols, and the inner layer of neutral fats. When the content of the gland is extruded through the duct and conveyed to the hair follicle, the regular arrangement disappears and the three products fuse.

Sweat secretion.—Fowle *et al.* (88) recommend a colorimetric quantitative method for the measurement of insensible perspiration from small skin areas, based on the color change of cobaltous chloride by moisture, and called "the perspiration test patch."

For testing the local sweat response in human skin, Kahn & Rothman (89) used intradermal injections of acetylcholine bromide and visualized the appearance of sweat droplets by Minor's starch-iodine method. They found a remarkable sex difference in this sweat response, women being much less responsive than men. They also studied the sweat responses of denervated skin areas on sympathectomized patients and on cats after section of the sciatic nerve. Acetylcholine, according to the neurohumoral theory, is the chemical mediator of sweat nerve impulses and is supposed to act directly on the sweat gland cells independently of their innervation. Therefore, it was expected that denervation would not influence the action of locally injected acetylcholine. Instead, it was found that the sweating response became weak or absent a few hours after nerve section in the corresponding skin area and remained so during the observation period for several months. The authors could not explain the decrease of the sweat response after denervation, but they presented evidence showing that it was not due to degeneration of sweat gland cells. Without being able to prove it, they advanced the theory that a decrease of the permeability of cell membranes in the sweat glands might have occurred after denervation, thereby inhibiting the penetration of intradermally injected acetylcholine into the cell.

Richter & Whelan (90) studied the nature, intensity, and frequency of the nervous impulses which reach the sweat glands from

the sympathetic nervous system. They stimulated the sympathetic chain near L2 and L3 in cats by a faradic current and registered the galvanic skin response from the central pad of one of the hind feet. Single shocks caused single monophasic responses; if repeated shocks were applied with increasing rate, the responses showed an increasing tendency to fusion. With stimulation at 375 per min. the responses were completely fused. Inasmuch as painful stimulation causes monophasic currents in human beings, such stimulation probably causes only a single discharge to pass down the sympathetic chain to the sweat glands. With more prolonged stimuli, such as emotional excitement, the galvanic response in human beings tends to full fusion. From experiments in cats it can be concluded that in man the rate of nervous discharges to the chain must be greater than two to six per second in order to cause fusion of the galvanic response. This rate is far below that needed for fusion of contractions in striated muscle.

Whelan & Richter (91) mapped out the regional differences of electrical skin resistance in human beings. They described a pattern on the face with lowered resistance in the regions of eyes, nose, and mouth, and a narrowing of this area during sleep and in a cold environment. Relatively low resistance was noted also on hands, feet, axillae, and antecubital fossae. In agreement with these authors Shumacker (92) stated that areas deprived of their sympathetic innervation can be mapped out with greater accuracy by resistance measurements than by determinations of skin temperature.

Much attention has been paid to the excretion of vitamins by the sweat glands. During the period here under consideration, several studies were published on this subject (93, 94, 95). The presence of thiamine, riboflavine, pantothenic acid, and nicotinic acid in sweat was demonstrated. Ascorbic acid was found by one group of workers (93) but not by others (95). From the available data it was calculated that in cases of prolonged profuse sweating the loss of vitamins with the sweat may amount to 5 to 10 per cent of the daily thiamine intake and to 3 to 5 per cent of the riboflavine intake (94). Losses of other vitamins with the sweat were found to be of no physiological importance. Some analytic results indicated that the concentrations of thiamine and ascorbic acid in the sweat are very much higher than in the blood. These data would indicate the active secretion of these vitamins by the sweat glands if, in

the given experimental arrangement, the evaporation of sweat during its collection could be avoided. The great variation of and disagreement in the published data show that it is not quite easy to eliminate this experimental error.

Yet exceptionally well controlled work in this domain was presented recently by Mickelsen & Keys (96). First, they endeavored to avoid the evaporation of water from sweat during its collection by use of a special device; and, second, they eliminated errors in the fluorometric estimation of thiamine and riboflavine. With their method only vanishingly small amounts of thiamine, riboflavine, and ascorbic acid were found in human sweat, whereas nicotinic acid was present in the order of 1 mg. per liter.

The same authors also presented valuable data on the amount of chlorides and of nitrogenous compounds in sweat from different regions of the body surface. Their determinations confirmed earlier data indicating that lactic acid and urea are much more concentrated in the sweat than in the blood. The chloride concentration was found to be higher in hand sweat by 30 to 70 per cent than in the total body sweat formed at the same time. Moderate variation in the concentration of chloride in the blood plasma did not influence the otherwise highly variable concentration of chloride, an indication of active secretion of chlorides by the sweat glands.

Vascular reactions.—In an extended series of experiments Di Palma *et al.* (97, 98, 99) studied the reactive arterial hyperemia which follows pressure-ischemia of the skin. Their most remarkable observation (100) was that in castrates and eunuchoids the reactive hyperemia was more variable than in normal men, usually appearing more suddenly and being greater in extent. Administration of testosterone and to a lesser degree of androsterone brought the reactions closer to normal.

Levinson & Essex (101) studied the effect of traumatic shock on the small blood vessels of the ear in rabbits. Shock was produced by intestinal manipulation, and the cutaneous blood vessels were examined under a compound microscope. The earliest change was a spastic constriction of the arterioles equally in ears with unimpaired nerve supply or ones denervated previous to the experiment. In normal ears the vasoconstriction led temporarily to a complete circulatory arrest, while there was no complete cessation of blood flow in the denervated ear.

Abell & Page (102) studied the effect of renin, angiotonin, ty-

ramine, and methylguanidine sulfate on the arterioles in the ear of the rabbit. In small doses all these pressor agents caused arteriolar constriction, while the capillaries and venules appeared unaffected. Arteriolar constriction as elicited by epinephrine or pitressin was more severe and lasted longer than that caused by angiotonin. In contrast to angiotonin, epinephrine and pitressin effected also contraction of venules.

A remarkable behavior of the cutaneous capillaries after bombardment of the skin with neutrons by means of the cyclotron was reported by Larkin (103). In the exposed erythematous area the vasoconstriction in response to scratching persisted considerably longer than in untreated skin. When histamine in 1:300 dilution was injected into the treated skin, no wheal formation occurred. Individuals with factitial urticaria (dermographia elevata) showed little or no urticarial response to mechanical stimulation in the treated area. The nervous mechanism controlling flare formation was not affected by the irradiation. The erythema and the changes in capillary reactivity appeared ten days after exposure.

Lewis' new work on the vascular axon reflex in the skin (104) was prompted by observations and studies on a patient afflicted with urticaria. This case, like the "cholinergic urticaria" case of Grant *et al.* (105), responded with local wheal formation to the percutaneous electrophoretic introduction of pilocarpine or of a stable choline ester (carbamylcholine), and with generalized urticaria to the systemic administration of carbamylcholine. Lewis concluded that in this case, as well as in that of Grant, the skin responds with increased susceptibility to a normal release of acetylcholine. An entirely new feature in Lewis' case, however, is that the flare around the urticarial wheals which were produced by heat, freezing, faradization, pressure, or histamine, was sprinkled with small satellite wheals. Infiltration anesthesia, nerve block, and procaine-barrier experiments revealed that these satellite wheals depend upon a local (axon) reflex as does the flare. Flare and satellite wheals still formed when the nerves were disconnected from the central nervous system but were abolished as soon as sufficient time had elapsed for these nerves to degenerate.

Lewis suggested the following interpretation: On stimulation of cholinergic nerves the acetylcholine released at the nerve endings primarily causes local liberation of H-substance and formation of the central wheal. Secondly an axon reflex is set up in the

ramifications of the cholinergic fibers, and again a release of H-substance occurs at the terminations of the axon reflex. This secondary release manifests itself in wheal formation within the area of the flare only in persons who respond abnormally to acetylcholine. Earlier, evidence that the nerves concerned in the axon reflex of the flare are identical with the "antidromic" posterior root fibers, and are cholinergic, had been presented. However, there is no reason to assume that these fibers are sensory (pain) fibers even if both have the same pathway. Together with the vascular reaction caused by local injury or by nerve stimulation a local hyperalgesia develops in the same territory by an axon reflex mechanism. This hyperalgesia has been hypothetically attributed by Lewis to a "nocifensor" nervous system which is independent of the sensory system. The balance of evidence, according to Lewis, appears to favor the assumption that antidromic impulses and axon reflexes are carried in a special ("nocifensor") and not in sensory (pain) nerve channels.

The blood serum of Lewis' urticaria patient caused urticarial wheals when injected intradermally into normal subjects.

Deutsch & Nadell (106) endeavored to develop a test to determine the responsiveness of skin to autonomic nerve impulses by introducing mecholyl or epinephrine electrophoretically to small areas of the skin and observing the local reaction to histamine in these areas. Individuals who showed intensified reaction to histamine after treatment with mecholyl were regarded as "cholinergic"; others in whom the reaction was greater after application of epinephrine were classified as "adrenergic."

Lambert & Rosenthal (107) continued their series of experiments on liberation of histamine or histamine-like substances, and demonstrated their presence by biological assays of dialyzed skin extracts following cutaneous injuries such as burns and chemical irritation. Similar results were reported by Haas (108).

Capillary permeability.—A great number of studies dealt with the various factors influencing capillary permeability.

In blood plasma, serum, and lymph obtained from the mechanically injured or burnt extremity of the dog, the presence of a toxic substance was demonstrated which produced an increase in cutaneous capillary permeability to intravenously injected dyes in normal dogs (109).

Earlier reports on the action of adrenal cortical extracts and

hormones on the capillary wall resulting in a decreased permeability to dyes were confirmed by several authors. The question whether this action is significant in the therapy of shock continues to be controversial. Fine & Fischmann (110) found that the diffusion into cutaneous tissues of intravenously injected dyes was markedly delayed after the administration of desoxycorticosterone acetate. But at the same time the authors could not observe any change in the diffusion rate of potassium thiocyanate, or any change in the size or duration of histamine wheals under the influence of cortical hormones. Therefore, they concluded that the effect of cortical hormones on the diffusion of dyes does not consist simply of an alteration of capillary permeability.

The capillary damage and increased permeability caused by intradermal injections of either peptone (111) or leukotaxine of inflammatory exudates (112) could be counteracted by adrenal cortical extracts as shown in diffusion experiments with intravenously injected trypan blue. The isolated hormones of the adrenal glands had a similar but weaker effect on capillary permeability, compared to adrenal cortical extracts.

Percutaneous absorption.—Rothman (113) recently published a review of the principles of percutaneous absorption, covering the literature of the years from 1920 to 1942. From the available data he arrived at the following conclusions:

Overton's rule which postulates that lipid-soluble substances enter the living cells, and that lipid-insoluble do not, is largely valid as far as percutaneous absorption is concerned. The impermeability of the skin to water and electrolytes is caused neither by the presence of a greasy-waxy cover of the skin nor by the presence of the horny layer. The seat of the absorption-barrier is to be placed in the transitional layers between cornified and non-cornified epithelium, i.e., in the stratum granulosum and stratum lucidum, which represent an electric double layer with positive hydrogen ions on the outside and negative hydroxyl ions on the inside. The presence of appendages in the skin complicates the mechanism of percutaneous absorption, mainly because any substance may penetrate into the follicular canal and reach the duct of the sebaceous glands and from there the gland cells, thus avoiding the passage through a stratified epithelium and directly contacting cells whose permeability is higher than that of the granular layer of the epidermis. If there is any absorption of lipid-insoluble

electrolytes the route is through the appendages. Ointments are helpful in bringing the incorporated substances closer to the surface of absorbing cells; this task is the more easily performed the more supple the ointment is. However, there is no evidence that either ointments or any other kind of "vehicle" may serve as a transportation vehicle into the cell itself. Choosing a substance to which the skin is completely impermeable, one will be unable to enforce absorption with any kind of ointment. Lipoid solvents, however, such as ether, chloroform, etc., enhance the permeability of the skin by disintegrating the lipoid frame of the cells, thus creating nonphysiological conditions. Similarly saponins which precipitate cholesterol will break up the barrier of cutaneous absorption.

By the use of galvanic current to introduce substances into the skin under the usual conditions of medical electrophoresis, the absorption through appendages will be tremendously increased, but the impermeability of the epidermis will remain unchanged. Under extreme conditions the electrophoretically introduced substances will penetrate through the follicular wall sideways and enter the epidermal cells from there, but the surface epithelium will not be broken through.

The articles published since the appearance of this review are in accordance with the principles stated above. Mandelbaum & Schlesinger (114) showed by means of the dark adaptation test that the fat-soluble vitamin A easily penetrates human skin. Zondek (115) recommended the percutaneous application of *p*-chloroxylenol for urinary antisepsis after having demonstrated its absorption through the skin and its excretion with the urine. The enhancing effect of lipoid solvents on absorption was demonstrated by Emmens (116), who showed by means of biological tests that male and female sex hormone preparations are more easily absorbed by the skin from ether, benzene, and alcoholic solutions than from lanolin and oil. Solomon (117) demonstrated with histochemical methods that electrophoretically introduced copper salts, in addition to their diffusion in the horny layer, penetrate through the follicle.

Oxygen consumption.—Amersbach *et al.* (118) measured the oxygen uptake of normal human skin in the Warburg apparatus. Their Q_{O_2} values were extremely variable, with a maximum of 2.36 and a minimum of 0.44. The difficulty of obtaining more

consistent results is obviously due to the fact that skin specimens of equal dry weight contain varying amounts of connective tissue, the respiration of which is negligible as compared to that of the epidermis. The latter contributes little to the total weight but is decisive in the rate of the oxygen uptake. By means of the method of Baumberger *et al.* (119) (see page 219) one will probably be able to obviate this difficulty. In spite of greatly varying normal values, Amersbach *et al.* succeeded in showing that in precancerous and cancerous lesions the Q_{O_2} was lower than that of the normal skin.

Cook *et al.* (120) found that phenylmercuric nitrate in a 1:100,000 aqueous solution decreased the respiration of rat skin by 24 per cent. If an aqueous-alcoholic yeast extract was added *in vitro*, the depressing effect of the germicidal agent was overcome without impairment of the antiseptic action. The yeast thus seemed to protect the host against toxic effects of phenylmercuric nitrate without lowering its germicidal power.

Butcher (72), working on underfed rats, reported that the Q_{O_2} of the skin of such animals is 0.9. In a preoperative period this value remained unchanged over several days. After adrenalectomy a steady rise of the Q_{O_2} was observed: at 46 hr. after operation by 14 per cent and at 66 hr. by 39 per cent (see also page 204).

Sensory perceptions.—In a critical review Walshe (121) discusses facts and theories relative to cutaneous sensibility. Recent anatomic investigations of Woollard & Weddell and of Tower (122a), and the electrophysiological studies on cutaneous sensory functions [see also Adrian (122)] lead Walshe to the conclusion that the physiological unit of sensory reception comprises all the end-organs innervated by the branches of a single posterior root fiber: the stimulation of a single end-organ will lead to antidromic impulses through all peripheral ramifications so that all end-organs belonging to that fiber will be involved. Walshe does not see any evidence for any kind of a dual peripheral mechanism of pain, as is postulated in Head's theory, in Lewis' theory of a nocifensor nerve system, and in the theory of two kinds of pain fibers of different conduction velocity. All cutaneous pain, says Walshe, arises in the rich ramifications of the intraepithelial free nerve endings, and theories on different qualities of pain "come to grief when they make contact with the hard facts of anatomy." Modern research, however, seems to support the doctrine of specific nerve energies

with four primary modes of cutaneous sensitivity, touch, pain, cold, and warmth. The specificity involves the entire sensory pathway, the end-organs having selective excitability, the fibers carrying impulses of different potentials and conduction rates, and the center modifying each category of sensory impulses.

The reviewers believe that the theory of identity of all pain sensations on an anatomic basis as represented by Walshe cannot be carried through consistently. The double pain sensation hardly can be interpreted in any other way than by the assumption of two separate pain fiber sets with different conduction rates. Concerning itching sensation, Walshe himself states, on the basis of Pritchard's work, that it "is probably a variant of pain sensitivity." Lewis (104), although not saying so, might have referred to the criticism of Walshe when he wrote:

... because the starting up of pain seems to depend on stimulation of naked nerve fibrils, I am not prepared to accept ... that all (these) fibres are pain fibres. ... The histological specimens show a baffling complexity of interlacing cutaneous nerves. It is quite beyond possibility to trace each and every fibre to its appropriate terminal. ... With such complexity of nerves, argument by exclusion appears to be a precarious method.

Chemical constituents.—Cornbleet *et al.* (123) estimated the calcium, potassium, and sodium content of normal human skin (epidermis plus corium) in ten individuals. Their maximum, minimum, and average values are summarized in Table I.

TABLE I
THE POTASSIUM, CALCIUM, AND SODIUM CONTENT OF NORMAL HUMAN SKIN*

	Max.†	Min.†	Aver.†
Potassium	252.2	240.7	247.0
Calcium	45.2	40.7	42.8
Sodium	352.1	347.4	350.0

* From Cornbleet *et al.* (123).

† The values represent mg. per 100 gm. of dry weight.

At the site of wheals produced by histamine or by stroking, and in spontaneous urticaria, the potassium, calcium, and sodium content of the skin was slightly lower than normal. Decrease of potassium was also found at the sites of other injuries, and this finding was tentatively interpreted as resulting from an outflow of potas-

sium from the injured cells. Oral administration of potassium chloride caused a decrease in sodium content of the whealed skin and an increase in potassium content in normal and in whealed skin.

McCardle, Engman & Engman (124) examined the mineral content of the human skin under normal and pathological conditions by means of spectrophotometric analysis in a study of 169 biopsy specimens. Their values on calcium, copper, magnesium, iron, phosphorus, and zinc were expressed in relative intensities of spectral lines. Comparatively large amounts of magnesium were found in the skin of normal persons; whereas the magnesium values were conspicuously low in affected and unaffected skin specimens of patients with chronic disseminated neurodermatitis. The authors discovered no relationship of the copper content of the skin to pigmentation. They stated that zinc is a constant constituent of the tegument. In a more recent publication Engman & McCardle (125) described a dermatitis in magnesium deficiency of albino rats.

Danckwortt (126) found in sheep wool 1 to 3 mg. lead per 100 gm. of hair. The values for cow hair were 0.6 mg. on the average.

Cornbleet (127) determined the protein, sodium, and chloride content in the blood plasma and in blister fluid and found that the ratio of the values were in conformity with the Donnan equilibrium.

Analyzing the chemical constituents of the skin in adult albino rats, Haldi *et al.* (128) noted a remarkable sex difference, consisting of a higher fat content and lower protein and water content in females as compared with males. There was a marked influence of the diet on these constituents as shown in Table II.

TABLE II
THE WATER, FAT, PROTEIN, AND GLYCOGEN CONTENT OF THE SKIN OF
ALBINO RATS ON VARIOUS DIETS*†

Diet	Males				Females			
	Water	Fat	Protein	Glycogen	Water	Fat	Protein	Glycogen
Stock.....	60.3	6.6	29.6	0.073	51.1	12.0	25.0	0.064
High carbohydrate ration.....	55.1	9.3	28.3	0.069	43.7	20.1	23.5	0.045
High fat ration.....	55.4	17.6	24.5	0.075	39.2	31.6	19.4	0.050

* From Haldi *et al.* (128).

† The values represent percentages of wet weight.

pH of the skin surface.—Draize (129) determined the pH of the skin surface in white and colored human beings, and in six species of common laboratory animals by means of the glass electrode method. In man he obtained the following acidity values: white males, maximum 4.70, minimum 6.26, average 4.85; white females, maximum 4.70, minimum 6.66, average 5.50; Negro males, maximum 4.39, minimum 6.63, average 5.21. In animals the average values were: guinea pig 5.50, monkey 6.42, cat 6.43, rat 6.48, rabbit 6.71, and dog 7.52.

Harry (130) performed pH determinations in various areas on the human skin surface both in male and female subjects. The values varied from 4.13 to 6.62 with an average of 5.4.

Arnold (131) studied the relationship between the normal bacterial flora and the pH of the skin surface. Alkalinization, exposure to warm water or to humid air increased the bacterial count, while acidification decreased it. The bacterial flora returned to normal density when the horny layer regained its original pH. Such buffering effect required about one-half an hour after alkalinization with 1 per cent sodium carbonate and about two hours after acidification with 1 per cent hydrochloric acid. Arnold compared the horny layer to a colloidal gel structure in which alkalinity causes uptake of water, but acidity leads to dehydration. He relates the changes in bacterial flora with the pH to these variations in water content. [See also the work of Whitcomb *et al.* (132).]

Techniques.—Several new methods were described to separate the epidermis from the dermis. Baumberger *et al.* (119) succeeded in carrying out this separation by heating the skin for two minutes at 50° C. on a paraffin oven with the dermal surface facing the plate. This procedure caused a temporary loosening; the epidermis could be easily removed in a continuous sheet by blunt dissection. If not promptly removed the epidermis became affixed again to the dermis. By treating the skin with isosmotic ammonium hydroxide solution for thirty-five minutes, they also achieved separation. By the use of different concentrations of ammonium hydroxide the epidermis could be separated either in its entirety or distally to the basal cell layer. An opportunity was thus afforded for a chemical comparison of the basal layer with the whole epidermis. Medawar (133) worked with Thiersch grafts; incubating them in an 0.5 per cent solution of trypsin at pH 8 and at 37° C. for one hour, he obtained complete separation of the epidermis from the connective tissue.

With any of these three methods the epidermal cells retain at least some of their vitality, as shown by respiration experiments. However, it is obvious that the heat technique of Baumberger *et al.* is far superior to any other technique hitherto described. It entails a minimum of alteration in the chemical composition and in the physiological functions of the cells. Apparently it damages only the connecting substance between the collagenous fibers and the interlocking finger-like projections of the basal cells, and even that change is reversible. The method, therefore, represents an important contribution to biological studies on the skin-parenchyma, e.g., studies on respiration, mineral metabolism, and lipid metabolism of the epidermis.

That most laboratory animals do not respond with blister formation to physical and chemical stimuli which elicit bullous reactions in man made for a great difficulty in experimentation on animal skin. Mirsky & Goldman (134) reported that the duck's skin after the feathers are plucked forms large bullae in response to a great number and variety of irritants. The separation of layers occurs in most cases at the dermal-epidermal junction.

Becker (135) published histological studies done with his modified technique of the dopa reaction. This technique was tested on one hundred twenty-one biopsy specimens from cutaneous lesions. Positive dopa reactions appeared in only 64 per cent of those cases which were positive with the original frozen section technique. Becker's method allows embedding in paraffin after the dopa reaction has been performed on the biopsy specimen, and it has the great advantage of permitting more exact cytological studies on thin paraffin sections than does the frozen section method. Kelley & Williams (136) developed a technique for the measurement of the oxidation-reduction potential of the skin surface by means of glass electrodes which are connected with a pH meter.

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DIGESTIVE SYSTEM¹

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Saliva.—A study in the monkey of the distribution of medullary points, the stimulation of which yields salivary flow, has revealed an excitable region comprising the dorsal midline area between the genu of the facial nerve and the hypoglossal nucleus, and extending laterally and ventrally through the reticular formation to the exits of the seventh and ninth nerves. While overlap exists, responses of the submaxillary gland are elicited predominately from the rostral part of the excitable area and those of the parotid gland from the caudal part. The reactions are almost entirely ipsilateral and are ascribed to the activation of the salivatory motor nuclei and their efferent root fibers (1).

Mean values ranging from 0.08 cc. to 0.88 cc. per min. have been obtained upon measurement of the adult human salivary secretion occurring in the absence of obvious external stimuli (2).

The measurement of nitrogen clearance from blood and saliva by means of a microgasometric technique during a period of breathing of tank oxygen revealed that 80 to 90 per cent of the nitrogen was cleared within the first ten minutes. The values for blood and saliva were comparable throughout the series (3).

Gastric secretion.—Recent reviews (4, 5) present evidence to substantiate the carbonic anhydrase theory of acid formation by the parietal cell of the stomach and suggest oxidation of glucose as the mechanism for the source of the energy. The mechanism or reaction by which the hydrogen ion is separated and secreted is as yet unexplained. Another comprehensive review (6) formulates a premise of membrane hydrolysis of neutral chlorides with simultaneous separation of the hydrochloric acid so formed to account for the secretion of acid. A study of the electrical energy output of the resting stomach (7) suggests that the stomach potential is inherently capable of producing sufficient energy for the secretion of gastric juice.

Urogastrone, a substance extracted from urine, administered intravenously to completely enterectomized dogs effectively in-

¹ This review pertains to the literature covering the interval of July 1942 to July 1943.

hibited the volume of gastric secretion and the output of free acid in these animals, a constant secretion having been previously obtained by the injection of histamine (8). This inhibition of gastric secretion was obtained in the absence of the small intestine, and the authors believe, therefore, that it is improbable that urogastrone acts by liberating enterogastrone.

A gastric secretory depressant obtained by precipitation with alcohol from gastric juice from pouches of animals immunized to human gastric juice produces an inhibitory effect upon gastric secretion when administered hypodermically (9). A similar precipitate obtained from patients not having carcinoma or pernicious anemia produced a transitory achlorhydria in 90 per cent of the experiments. The factor obtained from achlorhydric patients was present in high concentration. The method used for the extraction of urogastrone from urine did not extract the gastric secretory depressant from an alcohol precipitate of human gastric juice (10).

Histamine acid phosphate and histamine dihydrochloride in beeswax-mineral oil suspension when given intramuscularly to dogs with Heidenhain pouches exhibited a prolonged and intense stimulating action (11). The pouches secreted gastric juice for twenty-four hours or more and the volume of gastric juice obtained was many times greater than that obtained when histamine in comparable amounts was administered in saline suspension.

Thymoxyethyldiethylamine (929F) did not depress the secretory effect of pilocarpine upon the flow of gastric juice. The injection of 2,3-N-phenyl-N-ethyl, N-diethyl, ethylenediamine (1571F) depressed the histamine and pilocarpine induced flow of gastric juice. The drug does not modify the gastric secretion due to food (12). When these substances were used on dogs with Heidenhain pouches they did not exhibit demonstrable specific histamine antagonism to the gastric secretory response due to histamine (13).

The introduction of acid into the duodenum of dogs with Pavlov pouches and gastric and duodenal fistulae was found to inhibit the gastric secretion produced by lean meat meals only when the acidity of the duodenal contents was as great as pH 2.5 or more. The acid was introduced into the duodenum at a constant rate during various periods after ingestion of the meal. The extent of the depression of the gastric secretion was dependent upon the level of the pH produced (14).

Animals with jejunal transplants (pedicle grafts) in the an-

terior stomach wall fail to respond in the usual manner to the stimulation of gastric secretion by histamine. Gastric analysis made before and after the transplants revealed the combined and total acidities to be lower in each instance after the transplants (15). Similar studies have indicated transplants from the ileum and colon to be without effect in the inhibition of the development of an acid pH of the gastric mucosa following histamine; however both duodenal and jejunal grafts were effective (16). The conversion of a gastroenterostomy into a jejunal graft caused a reversal of the normal response to histamine in five of six animals (17).

A male subject with a permanent gastric fistula has been studied in an effort to correlate vascular changes in the gastric mucosa with changes in motility and secretion of this organ, direct observation of both the gastric mucosa and a collar of gastric mucosa around the stoma being possible (18). Histamine administration to this man was attended by an observable increase in blood flow, motility, and acid production. Alcohol produced a hyperemia and accelerated secretion, but the effects were observable only after the alcohol had been at least partially absorbed. The pleasurable anticipation of eating produced a hyperemia and hypermotility. Changes in vascularity as judged by color of the mucosa were always associated with changes in secretory activity, i.e., low acid output and pallor of mucosa.

No significant alteration of acid gastric secretion has been noted after ligation of two or three of the large arteries supplying the stomach of the dog (19), nor has the gastrosopic appearance of the mucosa been altered by this procedure. Ligation of the four large arteries to the stomach caused death.

Atropine administered in doses of $\frac{1}{8}$ grain at three hour intervals during the night to fifty normal subjects and to fifteen with active duodenal ulcer has been demonstrated to have diminished the volume of secretion as well as the free and total acidity in both normal subjects and in patients with ulcers (20). The decrease in values was more pronounced in the ulcer group.

Radium has been used to control gastric acidity with favorable results in thirteen of fourteen cases treated (21). In a few instances there was a gradual return over a period of time to a normal level of secretion in the treated individuals. The relationship of the state of tissue hydration and the acidity of the gastric secretion is reported to be one of decreased acidity during dehydration (22).

The simultaneous use of histamine and Liebig's extract in normal dogs has caused an increase in the acidity of the duodenal bulb contents as well as an increase in the volume of the fluid. These changes are believed to be due to gastric hypersecretion and rapid gastric evacuation. Interference with the neutralization in the duodenum occurred (23).

The marked depression of gastric secretion and the delayed gastric evacuation time observed after placing hypertonic solutions of glucose in the duodenum is believed to be due to altered osmotic conditions in the duodenum and not due to a hyperglycemia, since the slow intravenous administration of hypertonic glucose was attended by no significant alteration in gastric function (24).

In dogs with Pavlov pouches and with practically complete dysfunction of the posterior pituitary a normal gastric secretory response to the injection of pitressin tannate into dogs after pituitary stalk section tended to raise the volume of gastric secretion to normal levels without altering the acidity (25).

Of the several tests suggested for use in the differentiation of vagal and nonvagal gastric pouches, the insulin hypoglycemia test was found to be the most reliable (26).

The introduction of an amino acid mixture into the stomachs of eighteen subjects reduced the pH value of the gastric contents to a degree less than that usually considered to indicate the presence of free acid (27).

Half of the heavy water (deuterium oxide) introduced into stomach pouches of animals was absorbed in twenty minutes (28). There was no observable difference in the rates of absorption from the antral pouches and the fundic pouches, nor was any significant difference in the rate of absorption of this heavy water observed in secreting or resting stomachs.

Radioactive sodium was absorbed in small but significant quantities from fundic pouches of the dog, and absorption was more rapid when the stomach was in the resting state than when it was secreting (29). Absorption from antral pouches was greater per unit of surface area than from the fundic region. The state of activity of the mucosa made little difference in the absorption of radioactive sodium in the antral region. Variations in osmotic pressure of the sodium solution and in electrolyte concentration

in the blood serum within the limits observed had no significant effect on the rate of absorption of the sodium.

Gastric motility.—The pyloric diagraph, a device designed to record the distance across the intact pyloric sphincter, indicated the quiescent sphincter either in the fed or fasting animal to be in the relaxed state (30). The sphincter usually exhibited motility, especially in the fed animal, and this motility took the form of rhythmic waves which progressed in an orderly sequence over the antrum, sphincter, and bulb. In general, the sphincter was relaxed for at least 60 per cent of the time. Sphincter opening is a characteristic phase of the cyclic activity, not fundamentally the result of a passive stretching produced by material propelled from an adjacent portion of the gut lumen. Gastric evacuation, fluoroscopically observed, normally began some time after sphincter relaxation was complete, and evacuation continued during the period of sphincter contraction.

The influence of hydrochloric acid on motor activity of the pyloric sphincter and the immediately adjacent portions of the gut has been investigated in the normal trained dog by a multiple balloon method and a fluoroscopic-optical manometer technique (31), and evidence has been presented to indicate that hydrochloric acid in the stomach exerts little or no physiological action on the motor activities and the pressure changes in the pyloric sphincter region, or on the process of gastric evacuation. Hydrochloric acid in the duodenum has been found to be moderately effective in suppressing the activities of the pyloric antrum, thus retarding gastric evacuation. The activity of the pyloric sphincter and the upper duodenum was also inhibited. Some duodenal regurgitation may result from the more complete inhibition of the antrum than of the duodenal bulb.

In health, gastric motor activity was found to consist of three phases designated as active contraction, tonus rhythm, and relative quiescence (32). No relationship between motility of the stomach and acid secreting power was found. In patients with peptic ulcer, gastric tone was increased and contractions were stronger than in healthy subjects. In subjects with gastric carcinoma contractions were less frequent and weaker than in the normal. In normal subjects the ingestion of cold water inhibited gastric contractions for ten to thirty minutes. No similar inhibition was noted in subjects with peptic ulcer.

Kymographic records made from the stomachs of children (33) revealed three types of gastric activity and emptying. One is described as the normal peristaltic type in which the emptying depends upon satisfactory filling of the prepyloric area, emptying being independent of position and hydrostatic pressure. In the second type, a state in which there was variable tone, the prepyloric filling was poor, and the gastric contents were passed unevenly. Emptying of the stomach depended somewhat on posture and internal hydrostatic pressure. In the third or abnormal type, the stomach emptied according to the hydrostatic pressure within it. When the viscus was in good position it filled and emptied rapidly. A small amount of the gastric contents was sometimes retained until the subject lay down, whereupon the residue usually passed into the prepyloric canal.

Vagotomy caused the abrupt cessation of the vigorous peristaltic activity previously initiated in the cat's stomach by feeding. The activity was not resumed during the period of observation which extended over several hours. A persistent diarrhea following the removal of the inferior mesenteric ganglion has been described (34).

The gastric emptying time of young adult males as observed fluoroscopically following a meal of barium and farina was found to range from 1.5 to 3.3 hours with an arithmetic mean of 2.13 hours (35). Similar observations (36) indicated that the addition of such carminatives as Fluidextract of Ginger, Tincture of Capsicum, and Oil of Peppermint in therapeutic doses to the meal seldom influenced the gastric emptying time of normal individuals. In the dog, Oil of Peppermint, dehydrocholic acid, and disodium phosphate used in therapeutic amounts also failed to alter the gastric emptying time significantly (37).

Depression of gastric motility and secretion has been observed (38) following the administration of certain pyrogenic substances in doses too small to cause a change in rectal temperature or to produce evidence of subjective signs in most of the animals used. Pentnucleotide and yeast nucleic acid exerted the most profound effects.

The gastric emptying time in rats, as determined by measurement of the residual gastric glucose at intervals after the intravenous (39) and oral (40) administration of acutely intoxicating amounts of ethyl alcohol, is significantly prolonged.

The introduction of bile into the quiescent stomachs of fasting

animals was followed by the appearance of typical hunger contractions. When introduced into stomachs during a contraction period, a very short interval of inhibition of activity was produced in about one-half of the animals used. The effect of bile was obliterated by atropinization (41).

The actions of various drugs upon the movements of the fasting stomach of man have been studied by a modification of a balloon method. Atropine in small doses produced an increase in gastric movements; larger doses, up to 1.0 mg. intravenously, produced an immediate cessation of gastric activity. Atropine did not alter the stimulating action of prostigmine on gastric activity and the atropine effect was not reversed by previous administration of prostigmine. Epinephrine administered subcutaneously in ordinary therapeutic doses produced a complete cessation of gastric motility lasting fifteen to sixty minutes. Calcium gluconate exerted a sedative action on the fasting contractions of the stomach (42). Thymoxyethyldiethylamine (929F) administered intravenously had no consistent effects on the spontaneous or postprandial activity of the stomach nor upon the motility of exteriorized loops of intestine (43).

Gastric emptying time has been found to be prolonged in dogs maintained for variable intervals in chambers under reduced pressure. There was gradual return to the normal emptying time in most animals as adaptation to the state of intermittent reduced oxygen tension occurred (44).

Gastrectomy.—Studies in patients with complete gastrectomies revealed normal protein digestion and fat metabolism (45). Partial and complete gastrectomies produced transient increased motility of the gastrointestinal tract which was followed by delayed motility due to sacrifice of the vagus nerve. Gastrectomy in growing monkeys prevented any further gain in weight and skeletal development (46). A patient with a partial gastrectomy performed fifteen years ago for a gastric ulcer developed a macrocytic hypochromic anemia which responded to liver therapy (47).

Peptic ulcer.—Measurement of the acidity of contents of the duodenal bulb and pars pylorus obtained simultaneously from fasting normal persons showed an average pH of 5.60 and 3.51 respectively, but no constant relationship was found between the two (48, 49). Free acid was generally absent from the contents of the duodenal bulb. The fasting duodenal acidity, with an average pH of 3.90, was found to be greater in patients with duodenal ulcer

than in normal persons (50, 51, 52). Direct visualization of the gastric mucosa in a patient with a gastric fistula revealed that stimulation by food, alcohol, histamine, or by emotional factors resulted in hypersecretion, hypermotility, hyperemia, and engorgement of the mucosa, the appearance suggesting hypertrophic gastritis. Removal of the protecting mucus and prolonged contact with acid gastric juice produced a chronic ulcer (53, 54). Duodenal ulcer distress was found to occur when both stomach and duodenum simultaneously or the duodenum alone exhibited motility, but no pain occurred when the duodenum was quiescent (55).

Extracts of urine of normal pregnant and nonpregnant women exhibited prophylactic and therapeutic properties on Mann-Williamson ulcers in dogs, such results being unobtainable from urinary extracts from patients with duodenal ulcer (56). The healing effect of urinary extracts was not due to the presence of prolactin (57).

Formation of peptic ulcers, produced in a number of laboratory animals by the injection of histamine in beeswax, was not inhibited by pregnancy (58). No relationship was found between blood histamine and the presence or absence of free hydrochloric acid in the stomach of patients with peptic ulcer and with gastric carcinoma (59). Administration of histaminase to dogs which had been fed cinchophen did not prevent the development of peptic ulcers (60). Ulcerations were produced in chick gizzards by deficiency diet or by the administration of cinchophen (61). Addition of the antigizzard-erosion factor to the diet modified or prevented such ulceration in the chick.

Ingestion of the antacids calcium carbonate, aluminum phosphate, and aluminum hydroxide in the treatment of peptic ulcer did not disturb the acid-base metabolism appreciably (62). The electrolyte composition of the blood was not altered.

Examination of the gastric contents of patients with perforated peptic ulcer demonstrated a low hydrogen-ion concentration at the time of operation (63). The gastric acidity usually returned to normal in twenty-four to forty-eight hours. A rapid return to normal indicated a good prognosis. A review of favorable results of vagotomy, thus removing the cephalic phase of gastric secretory stimulation, is presented in patients with peptic ulcer (64). In a report of four thousand cases of patients with peptic ulcer the procedure of gastroenterostomy and ligation of four of the five

arteries supplying the stomach is advocated because of immediate reduction in gastric acidity and good end result (65).

Intestinal secretion and absorption.—The progressive increase in pH throughout the jejunum and ileum is due to an increase in bicarbonate and decrease in carbon dioxide tension. Ammonium chloride acidosis caused no significant alteration in the reaction of the intestinal contents; however, a bicarbonate alkalosis caused a rise in pH (66).

Alkaline phosphatase is secreted by the intestinal tract in varying but considerable quantities, the duodenum and jejunum being the major sites of secretion (67).

The changes in the blood sugar concentration, after the oral administration of thirty grams of glucose in concentrations varying from 5 to 30 per cent, revealed that the greatest rise in blood sugar concentration within thirty minutes of administration occurred when the lower concentrations of sugar were employed (68). Further, there was no appreciable difference in the rise of the blood sugar curve during the first thirty minutes regardless of the concentrations of sugar solution employed when the administered volume was kept constant. In one hour, the blood sugar concentration was highest with the higher concentration of sugar employed.

Absorption of iron from the hemoglobin of whole blood is not likely to occur unless the hemoglobin undergoes some degree of breakdown in the alimentary tract (69).

Metabolic studies of adults have shown that increasing the protein intake raises the amount of calcium and magnesium absorbed from the intestinal tract and subsequently excreted in the urine (70). The urinary excretion of calcium, magnesium, and phosphorus by a normal person rises and falls with the intestinal absorptions (71). Under the conditions of the experiments the presence of lactose or glucose and galactose did not increase the rate of calcium absorption (72). Essentially all of the phosphorus in the diet was rendered unavailable when aluminum sulfate was fed in amounts chemically equivalent to the phosphorus. When aluminum hydroxide was fed to young rats at levels of 0.5 and 1.0 per cent of the diet about one-third to one-fourth of the aluminum was converted to a form reacting with phosphorus (73). Absorption of diethylstilbestrol from the intestinal tracts of rats and cats was evident in as short a time as three minutes, and as far as

could be determined the effects were the same for diethylstilbestrol in suspension and in solution in the form of the sodium salt (74). The impaired absorption of glucose, evident in adrenalectomized animals under some conditions, is not referable to the lack of influence of any adrenal cortex hormone on the intestinal mucosa (75). Following the ingestion of glycine by subjects with gastric and esophageal carcinoma there was a delayed absorption and utilization of this amino acid (76).

Marked impairment of absorption of an enzyme hydrolysate of casein from a jejunal loop was noted in four of five patients with chronic idiopathic ulcerative colitis or enterocolitis (77). Active sprue is characterized by a failure of absorption which manifests itself in complete lack of elevation of the lipids and of the vitamin A content of the serum after the ingestion of a standard dose of butter or vitamin A (78). However, during a remission a fairly satisfactory fat and vitamin A absorption is found. In contrast to sprue cases of extensive granulomatous jejunoileitis show a fairly satisfactory fat and vitamin A absorption in the tests.

A device containing a test food substance has been placed in the human gastrointestinal tract at various levels by an intubation technique as an aid in the study of digestion and absorption (79). Results indicate that substantial proteolytic activity occurs in the normal stomach, and throughout the normal small intestine the concentration of proteolytic enzymes is sufficiently high to effect a very considerable amount of digestion regardless of the point at which the process begins. A special intubation technique has been used to show the upper small intestine to have a marked capacity for absorption of ascorbic acid (80).

Intestinal motility.—Longitudinal and circular layers of the rabbit intestine, suspended in Tyrode solution, were studied to learn the effects of drugs, sugars, and allied substances (81). Acetylcholine, muscarine, and eserine stimulated both longitudinal and circular layers. In glucose-free solution the effect on the longitudinal muscle disappeared, while that on the circular layer persisted. The addition of pyruvate to glucose greatly stimulated the longitudinal muscle. The effect on the circular muscle was small. Lactate stimulated mainly the circular muscle. Phloridzin inhibited the stimulating action of glucose but had no influence on the muscle response to lactate or acetylcholine in the absence of glucose. Atropine produced inhibition of longitudinal muscle

in glucose solution but this effect soon disappeared. Small doses of atropine abolished the stimulating effect of acetylcholine and of muscarine on longitudinal and circular muscles. The circular layer is less responsive to stimulation of glucose. The effect of pyruvate, mannose, and galactose is similar to that of glucose.

The response of segments of rabbit intestine from different levels to various chemical stimulants and depressants was compared (82). Segments of upper intestine were more sensitive to acetylcholine while those at lower levels were more responsive to epinephrine. This gradient of chemical activity was not observed with other stimulants or depressants that were studied. Propylene glycol in 1 per cent concentration had a stimulating action on the rabbit intestine *in vitro* (83). Progesterone in concentration of 1:256,000 or greater decreased both the tonus and amplitude of contraction, and this depression was increased by epinephrine.

The relation of inhibitory action of atropine and scopolamine to the nerve supply of jejunal segments in the dog was determined (84). Denervation by cutting the extrinsic nerves in the mesentery, by vagotomy, by splanchnicotomy, or by a combination of these appears to increase the inhibitory action of atropine and of scopolamine.

Bulbocapnine acts centrally and stimulates both sympathetic and parasympathetic mechanisms in the dog. Sympathetic effects were most important for intestinal motility, the amplitude of contraction being diminished. Vagotomy augmented contraction of intestinal loops just below the duodenum, but inhibited activity of loops just above the ileocecal valve. Splanchnicotomy activated the vagus effects. Bulbocapnine did not change the rate of intestinal contractions (85). Sensitivity of jejunal muscle segments to epinephrine was tested after vagotomy and after sympathectomy (86). Section of the vagus or of the preganglionic fibers had little effect. Section of postganglionic fibers produced a marked increase in sensitivity to epinephrine.

The inhibitory reflex arc of the small intestine of the dog is considered to be localized in the lower thoracic and upper lumbar spinal cord. Afferent fibers do not cross to the opposite side but make connections with the efferent neurones in the same side and segment of the cord. The reflex response is independent of the vagus or the adrenal gland (87). Studies on the brain of the cat indicate that inhibition of peristalsis in the stomach, intestines,

and particularly the colon can be produced by adequate stimulation of the lateral hypothalamic area (88). Motor responses of the gastrointestinal tract to proper hypothalamic stimulation were less definite.

Distention of the gall bladder in dogs had no effect on peristaltic activity of exteriorized loops of the small intestine. Distention of the urinary tract produced inhibition of activity of the gut as long as distention was maintained. This inhibitory effect was less pronounced in the upper segments than in the lower portion of the small bowel (89). Observation of exteriorized loops of ileum and jejunum in the dog after obstruction of the common duct revealed that during the first twenty-four hours after surgery there was decreased activity of the intestines (90). Quick return of activity reached the maximum peak in four or five days, and was followed by a gradual decline to a minimal level in twelve to fifteen days. Activity was gradually resumed but never to the normal level. Decreased intestinal activity was more noticeable in the fasting state. There appeared to be an inverse relation between the amount of serum bilirubin and changes in intestinal activity.

The combined effect of ether anesthesia and exploratory laparotomy in dogs with exteriorized intestinal loop abolished intestinal activity for four hours, but intestinal motility was almost normal at the end of twenty-four hours. Section and anastomosis of the intestine inhibited intestinal activity for about forty-eight hours. When the site of operation was proximal to the loop under observation, feeding inhibited activity in the loop. Intestinal activity became normal after the sixth postoperative day (91). Direct observation of the motility of the small and large bowel in patients undergoing various surgical procedures revealed a contrary action between the two segments (92). During contraction of the small bowel the colon was inactive. When the colon was contracting the small intestine appeared to be inhibited. Drugs that stimulated the motility of the small bowel inhibited the action of the colon. Posterior pituitary solution produced contraction of the colon but diminished the activity of the small gut. Postoperative distention was thought to be produced by morphine which stimulated the small intestine but inhibited the action of the colon.

An instrument is described for recording intraluminal pressures at multiple levels of the human digestive tract (93). The basic pressure in the human small intestine was found to be 8 to 10 cm. of water. Phasic pressures, occurring spontaneously, rose

to 30 or 40 or occasionally to 50 cm. of water. Placing the intestine under stress by obstruction or by giving morphine produced only slight increase in intraluminal pressure. It was observed that human subjects emptied gastric contents when the total intragastric pressure was at or near its peak rather than in time with prepyloric peristaltic contraction. Pressure waves affected the antrum and fundus alike and had no relation to gastric peristalsis. Rise in duodenal bulb pressure bore approximate relationship to the peak of intragastric pressure corresponding in time to the opening and closing of the pylorus.

Studies of motor activity of the small intestine in two patients with sprue show that the gut lacks the normal resistance to distention. Prolonged treatment with the whole vitamin-B complex produced only slight change. Observation of the effects of certain drugs on the intestinal motility suggested that the nervous mechanism of the small bowel in sprue failed to liberate active acetylcholine (94). Radiologic studies of dogs whose diet was deficient in either pantothenic acid or inositol revealed abnormal findings in the gastrointestinal tract characterized by hypermotility, hypertonicity, and segmentation of the small and large bowel (95).

Intestinal obstruction.—Edema of the bowel appeared to aggravate existing partial obstruction of the intestine, and motility has been observed to be markedly depressed when there is an associated edema of the bowel (96). Raising of the plasma protein concentration has restored small bowel activity and has aided in deflation of the patient.

In shock, produced by strangulation of a short loop of ileum, there occurred a large enough loss of plasma locally to account for the fall in blood volume and blood pressure (97). Intestinal obstruction at various levels in dogs produced a degree of dehydration sufficient to produce death. Hematocrit, plasma protein, hemoglobin, and available fluid determinations were made with the revelation that while hemoglobin, hematocrit, and plasma protein values indicate directional changes over short periods of time they cannot be used quantitatively to determine plasma or blood volume changes (98, 99). The deficit in total circulating plasma protein may be considerable in cases of intestinal obstruction especially in those of long duration, and this loss may be masked by hemoconcentration.

Intraparietal capillary flow in rat intestine continued until an intraluminal air distention pressure equal to 50 to 60 mm. Hg

was reached. Arteriolar and venular flow continued up to a distending pressure of 80 to 90 mm. Angulation or kinking of extraparietal vessels during distention permitted obliteration of capillary flow at values as low as 30 mm. After deflation, following distending pressure of 50 to 60 mm. maintained for two hours, there was recovery of flow in most capillaries (100).

Bile and biliary tract.—Cinchophen given to dogs with bile fistulas in doses of one gram per day over periods as long as thirty-three days did not act as an hepatotoxin (101). This dosage of the drug caused a marked hydrocholeresis with an increase in the cholesterol output. On a gram-weight basis cinchophen was three times as effective as a hydrocholeretic as was dehydrocholic acid.

After a single oral dose of half a gram of cinchophen to dogs the drug practically disappeared from the bile in sixteen hours, and none or only a trace of it was found in the bile after twenty-four hours (102). The concentration of cinchophen in the bile was quite constant regardless of the size of the dose used or the frequency of the dose. About 50 per cent of an oral dose of cinchophen was excreted in the urine of dogs, but none in the feces.

Sulfanilamide, sulfathiazole, and sulfadiazine did not pass through the wall of the vesicle of cystic duct occluded dogs to reach the gall bladder bile (103).

In normal unanesthetized dogs injection of ox bile or dog bile into the intestine did not increase the rate of secretion of pancreatic juice, and the amount of pancreatic juice secreted in response to stimulating foodstuffs was less when bile was present than when it was absent from the intestine (104). Absorption from the intestinal tract of steroid hormones following oral administration was equally effective in the presence or absence of bile (105).

Hepatic flow in about 70 per cent of the anesthetized dogs that were used was inhibited by distention of the proximal colon. The effect was obtained after decentralization of the celiac ganglion, after section of the vagi, after section of the splanchnic nerves, or after excision of the lumbar sympathetics (106).

The nerve pathway to the choledochoduodenal junction has been described as a gastroduodenal plexus lying between the gastroduodenal artery and the common bile duct, and as a gastroduodenal nerve directly from the hepatic plexus to the left of the duodenal artery. The rate of emptying of the bile passages after the ingestion of food was not altered by severance of the gastroduodenal plexus, but the rate of emptying was markedly retarded by

severance of the gastroduodenal nerve. Delay in emptying of the gall bladder followed severance of the right vagus, and acceleration resulted when the roots of the celiac ganglion were cut down to the second lumbar nerve (107).

Magnesium sulfate introduced orally or by duodenal tube acted upon the gall bladder and sphincter in the same way and for the same length of time as egg yolk. There was a difference in degree, the egg yolk obtaining the greatest response (108). Initially a dose of either egg yolk or magnesium sulfate usually caused the sphincter to contract and the gall bladder contraction to be interrupted, but by the end of the first four or five minutes the sphincter entered a period of progressive relaxation which lasted for an average of seventeen minutes. During this period the gall bladder began its main phase of contraction which lasted for an average of about thirty minutes. Because of the similarity in action of magnesium sulfate and egg yolk it is suggested that magnesium sulfate be considered, like egg yolk, a hormone-producing substance.

Study of the effect of food upon the sphincter of Oddi in human subjects showed that a fatty meal consisting of egg yolk and cream produced relaxation of the sphincter, a result not obtainable with fresh olive oil. A protein or carbohydrate meal had little effect upon sphincter resistance (109). Determination of the resistance of the sphincter of Oddi in the human and in dogs to the administration of drugs revealed a variable effect by the epinephrine group, and an inconstant one from papaverine (110). Sphincter resistance was increased by atropine, prostigmine, and codeine; and inhibited by trasentin, nitroglycerine, and amyl nitrite. Coughing, nausea, sight or ingestion of food, and passage of stool increased the sphincter resistance in the human.

Decreased fat appetite was observed in rats following ligation of the common bile duct, the animals preferring a high carbohydrate diet (111).

Liver bile collected from a patient with a biliary fistula showed no alteration in its quantitative composition when the bile was collected during total starvation or during feeding on a high carbohydrate mixture (112). Normal infants fed on high fat diets exhibited an increased output of urobilin in the feces, and the effect was independent of the type of fat fed (113).

Pancreatic secretion.—A substance, named pancreozymin and extracted from the small intestine, stimulates secretion of pancreatic enzymes and produces a response of the pancreas which is not

affected by section of the vagus and splanchnic nerves or by the administration of atropine (114). It is not affected by vasodilator substances and produces no hypoglycemic action. The substance is not present in the gastric mucosa. It is suggested that pancreozymin is the hormone in control of enzyme secretion of the pancreas.

Observation that total loss of pancreatic juice by external fistula does not produce a fatty infiltration of the liver suggested that lipocaic is not significantly present in pancreatic juice (115). Animals with complete severance of the pancreatic ducts developed marked fatty infiltration of the liver; while in animals retaining an accessory duct and a small amount of active pancreatic tissue, no evidence of fatty degeneration was found (116).

Depancreatized and duct-ligated dogs were fed meat and meat fractions in addition to a basic ration (117). Dogs receiving dried meat powder did not develop fatty infiltration of the liver. A raw meat diet or a meat powder plus meat extract diet resulted in a fatty degeneration of the liver. The same result was obtained by feeding meat powder and inositol. In four of seven dogs fatty infiltration was present after a diet of meat powder plus water extractives. The findings suggest that fatty infiltration of the liver can be produced by a substance present in meat.

When young rats were fed diets of varying composition, a high carbohydrate diet produced a pronounced increase in amylase content of pancreatic secretion and a decrease in trypsin (118). A high protein diet resulted in marked increase in trypsin content and a definite but less extensive increase in lipase. No alteration in lipase or trypsin content was noted on a high fat diet. A high fat, low protein diet produced a repression of all pancreatic enzyme formation, but 1 per cent of choline added to this diet increased the content of all the enzymes. Determinations of the enzyme content of pancreatic tissue and of the pancreatic juice were found to be comparable.

When olive oil and oleic acid were administered to depancreatized dogs, there was a varying degree of impaired absorption of neutral fat, some animals being able to absorb 75 per cent or more (119). The findings indicate that either hydrolysis was not essential or that the gastric and intestinal juices furnished considerable amount of lipase. Absorption of fatty acids was definitely impaired, and it is suggested that the pancreas acts in some other way than through the secretion of lipase.

During quantitative determination of enzyme activity in

normal subjects during fasting and after stimulation of pancreatic secretion with olive oil, it was observed that the use of the single tube technique of obtaining duodenal contents was as efficacious as the method of using the double tube (120). A system of evaluating pancreatic secretory activity is described and studies of enzyme activities in patients with various pancreatic and gastrointestinal disorders are recorded.

Physiological studies on a patient with an external pancreatic fistula revealed that meals high in carbohydrate and protein and low in fat stimulated greater flow of all components of pancreatic juice than high fat diet alone (121). Ephedrine sulfate and atropine sulphate diminished secretion of all components except amylase. Secretin plus mecholyl chloride produced the greatest secretion of all components of pancreatic juice.

Injection of acetyl-beta-methylcholine hydrochloride combined with eserine sulphate caused an increase in serum amylase and lipase when a normal pancreas was present but not when the pancreas was atrophic (122). Injection of small amounts of secretin produced no effect on serum lipase in the presence of a normal pancreas but evoked a rise of serum lipase when the pancreatic ducts were obstructed.

A study of pancreatic secretion in thirteen chronic diabetic patients free of any gastrointestinal disorders revealed diminution in volume of secretion as well as of total bicarbonate, amylase, and trypsin, the findings being correlated only with long duration of the disease (123). A review of the use of secretin as a test of pancreatic function is reported (124, 125).

Colon.—Studies of the motor innervation of the colon in dogs, pigs, and monkeys (126) show that the pelvic nerves are cholinergic, and electric stimulation causes contraction of the longitudinal and circular muscles of the descending and distal colon. The hypogastric nerves and the fibers of the celiac root of the inferior mesenteric ganglia are adrenergic and when stimulated electrically they cause circular contraction of the distal colon and descending colon, respectively, an effect not uniformly obtained. Electrical stimulation of the vagus nerve produces an ineffective response in the colon of the animals studied.

Motility studies by means of the tandem balloon in patients with colostomies revealed that colon activity may be propulsive or nonpropulsive (127). Different types of motility may occur in adjacent segments of the colon but coordinated action of these

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Motility studies by means of the tandem balloon in patients with colostomies revealed that colon activity may be propulsive or nonpropulsive (127). Different types of motility may occur in adjacent segments of the colon but coordinated action of these

segments is necessary for propulsion of the contents. When a strong propulsion wave occurred in a proximal segment and failed to pass a distal segment cramps developed. Stasis resulted when a segment did not receive propulsive waves. Colon motility was depressed by atropine and traserentin. The latter drug aided in restoring the normal gradient of the colon. A combination of solution of posterior pituitary, prostigmine, and ergotamine tartrate produced a prompt and sustained increase in propulsive motility of the colon without side reactions. Morphine induced an increase in the tonus and nonpropulsive motility.

Study of the fat excretion by the intestines of subjects receiving a fat-free diet indicated that the large intestine excretes more fat than the small intestine (128). Excretion of fat by patients with ulcerative colitis was less than by normal persons but greater than by patients subjected to a resection of the right half of the colon.

Miscellaneous.—Observation by means of an improved device for measuring blood flow in the human gastrointestinal tract revealed that gastric and duodenal contractions were accompanied by a transitory acceleration of blood flow. The acceleration was also associated with anxiety states and cephalic gastric stimulation, as well as with a prolonged effect induced by histamine (129).

Measuring the rate of flow from different duodenal tubes under various conditions, the important extrinsic factors were found to be the size of the lumen of the tubes, the length and amount of suction, as well as the total surface of the drainage openings and addition of the metal attachments to the outflow. The drainage efficiency varied at a suction of 90 cm. of water between 258 ml. and 70 ml. per thirty seconds and at a suction of 15 cm. between 71 ml. and 15 ml. The tubes examined exceeded at a suction from 60 cm. to 15 cm., the maximal natural inflow into the duodenum (130). Simultaneous drainage of the duodenum and jejunum showed that the escape of fluid during an adequate duodenal drainage is negligible and that quantitative efficiency of duodenal drainage could be achieved without the use of an obstructing balloon (131).

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LIVER AND BILE

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With the increasing attention to problems of immediate practical relation to the war effort, fewer articles bearing on the subject of this review have appeared. The curtailed output of foreign journals and the difficulty of obtaining those that have appeared have also diminished the volume of literature bearing on liver and biliary secretion available to the reviewer. It is interesting to note that interest in the deposition and metabolism of liver fat and the action of lipotropic and lipogenic agents has been well maintained, while the number of articles concerned with hepatic carbohydrate metabolism and some other aspects of liver function appears to have decreased.

HEPATIC LIPOGENESIS AND LIPOTROPISM

Best & Lucas (1) have presented a comprehensive review on choline and related factors, dealing especially with their chemistry and dietary significance; literature as late as that of 1942 is included.

There is continued disagreement concerning the presence or absence of a lipotropic factor in the pancreatic juice, a point which must be settled before the claim of Dragstedt and collaborators that lipocaic is an internal secretion can be finally accepted. Allen, Vermeulen, Owens & Dragstedt (2) present further evidence that complete absence of pancreatic juice from the intestinal tract does not result in deposition of liver fat if the pancreas is intact; these studies were made on dogs with pancreatic fistulae. Popper & Necheles (3), on the other hand, find that dogs with complete occlusion of the pancreatic duct show extensive fatty infiltration twelve months after operation. In two animals in which they occluded only the main pancreatic duct the major portion of the gland was atrophic about eight months postoperatively and only a small remnant in the neighborhood of the lesser duct appeared to be continuing to secrete into the intestine; these animals did not exhibit fatty livers. They conclude that a small fraction of the normal volume of pancreatic secretion is sufficient to prevent fatty

infiltration, but that complete absence of external pancreatic secretion will result in fat deposition; this is in accord with the majority of previous reports not originating from the University of Chicago group. Lipocaic was administered parenterally by Julian, Clark, Van Prohaska, Vermeulen & Dragstedt (4) to animals which received ketogenic hormone or were fasted; fatty infiltration could be prevented in either instance by lipocaic. They also found that the Houssay dog develops a fatty liver which responds to lipocaic. Lipogenesis after pancreatectomy is evidently not due to the unopposed action of pituitary hormones.

Several new factors concerned in the regulation of liver fat have been suggested. Fouts (5) has shown that choline alone is not adequate to prevent fatty livers in dogs fed diets containing 41 per cent casein even when the diet also contains added thiamine, riboflavin, nicotinic acid, pyridoxin, and pantothenic acid. However, when powdered liver extract was added to the above diet the fatty infiltration was prevented. Engel (6) finds that inositol, pyridoxin, and the essential fatty acids as well as choline must be present to prevent the occurrence of excess liver fat. According to Artom & Fishman (7), young rats placed on a low choline diet exhibit a decrease in the choline-containing phospholipids of the liver; the other phospholipids are little affected, and the neutral fat is increased. In newly weaned rats these effects could be completely prevented by supplementation with choline, ethanolamine, *dl*-serine, *L*-cystine, or *dl*-methionine, but in rats two to three months old these substances did not increase the amount of choline containing phospholipids. They also suggest that some additional factor is essential in maintaining the composition of the liver lipid on the assumption that such a substance might be present in newly weaned but not in older animals. The observation that prolonged pyridoxin deficiency (in pigs) produces fatty infiltration is confirmed by Wintrobe & Follis (8). If pantothenic acid is also lacking, growth is much impaired and the fatty liver does not appear. Evidence that generally impaired nutrition to the point of suppression of growth will inhibit fat deposition on diets otherwise lipogenic is also presented by Handler & Bernheim (9), who find that when growth on choline-deficient diets is suppressed by thiamine deficiency or by an excess of nicotinamide the regenerating portion of the liver is low in fat. The rate of regeneration of new liver tissue, however, is not affected. They suggest

that the suppression of fatty infiltration is due to an impairment of over-all metabolism which is not sufficiently severe to interfere with the regenerative process. A large amount of data on the effects of diet in depancreatized dogs and dogs with both pancreatic ducts ligated is presented by Ralli & Rubin (10), but the interpretation of their findings is somewhat difficult. The feeding of meat powder with the extractives removed prevented liver fat deposition in their animals, whereas if the extractives were given with the meat powder there was an increase in liver fat which did not persist beyond the fifteenth week. Raw meat was definitely lipogenic. The authors suggest that the fatty livers of such animals may be due to inability to digest and absorb raw meat, while meat powder can be utilized; they also interpret their results as indicating a lipogenic effect of the meat extractives and present some evidence indicating that inositol may be at least in part responsible for the deposition of liver fat when the extractives are fed. This is contrary to the previously mentioned observations of Engel (6). Honorato & Molina (11) gave vitamin K in the form of 2-methyl-1,4-naphthoquinone to rats on choline-deficient diets and found that the fat content of the livers remained normal and that the renal lesions were minimal as in choline-fed animals. The methyl group of vitamin K, although chemically quite stable, may therefore be labile in animal metabolism.

Lillie, Ashburn, Sebrell, Daft & Lowry (12) describe the histological changes in the liver on low protein, low choline diets. They conclude that the type of cirrhosis produced is not identifiable with any seen in man or produced by other experimental procedures; it is characterized by fatty infiltration with deposits of a hyaline-like substance that the authors term "ceroid." Correction of the diet results in regression of the fatty infiltration with persistence of fibrous trabeculations and "ceroid" phagocytes. Stetten & Grail (13) have found that the livers of rats on choline-deficient diets become low in choline, and that the proportion of lecithin in the fat is decreased. Feeding cystine or homocystine, on the contrary, yields a liver fat that is rich in lecithin; they conclude that there is no simple antagonism between the action of these amino acids and that of choline. Guanidoacetic acid administration causes a markedly fatty liver with a decreased choline content of the lipid, presumably because the transformation of the guanidoacetic acid to creatinine is irreversible and labile methyl

is used and excreted, which is not true when homocystine is converted to methionine. The same authors (14) have followed the half life of deuterium in liver fat, which is 2.6 to 2.8 days as compared with 5 to 6 days in depot fat; the presence or absence of choline in the diet had no effect. This indicates that when the fat content of the liver is increased in choline deficiency there is no failure to discharge the liver fat into the blood stream. According to Channon, Hanson & Loizides (15) the accumulation of fat on low choline diets is affected by the constitution of the dietary fat, being proportional to the content of C_{14} to C_{18} fatty acids that are given, while the solid unsaturated fatty acids have no influence. Earle, Smull & Victor (16) produced portal necrosis and cirrhosis within two weeks by feeding 12.5 to 15 per cent of cysteic acid in the diet; *DL*-methionine as 6.4 to 12.4 per cent of the diet caused severe atrophy but not cirrhosis, while 1 to 10 per cent taurine had no effect. They conclude that the hepatic lesions produced by cystine and cysteic acid are not dependent on the presence of the S-S linkage, oxidation of the sulfur, the formation of urinary sulfate (which was measured), or the presence of an amino group separated from sulfur by a 2-carbon chain.

METABOLISM

An ingenious technique for the study of hepatic heat production was applied by Fedorov & Shur (17), who inserted thermocouples through London cannulae into various abdominal vessels. The highest temperature was regularly found in the hepatic vein and the lowest in the aorta. Cooling the skin surfaces increased the apparent heat production of the liver, that is, the temperature in the hepatic vein rose relative to that in the portal vein and the aorta; a similar change accompanied the febrile state produced by heterogeneous transfusion or anaphylactic shock. The respiratory quotient of hepatic metabolism was determined by Chambers (18), using dogs in which the hepatic artery had been anastomosed to the portal vein so that while the oxygen saturation of the blood supplying the liver was presumably normal, a single sample of the blood entering the liver could be obtained and the necessity of any assumption concerning the relative amounts of blood delivered by hepatic artery and portal vein were avoided. When the dog had been fed a meat diet the hepatic respiratory quotient was above 0.7 and not significantly different from that of the whole animal.

In the starving dog, or when a high fat diet had been given, the hepatic respiratory quotient was quite consistently below 0.7. This confirms the impression previously gained from studies on hepatic tissue slices, that the liver is exceptional in that it may exhibit a lower respiratory quotient than is found in other tissues; this is presumably associated with the utilization of oxygen without a proportional release of carbon dioxide when acetone bodies are formed. Craig (19) finds that the oxygen uptake of rat liver slices is depressed 25 per cent on exposure to nitrogen when the rats had been fed, and 75 per cent if the animals had been subjected to a twenty-four hour fast. About 65 per cent of the hepatic tissue was removed from rats by Norris, Blanchard & Povolny (20), who observed that the rate and amount of regeneration varied inversely with the age of the animals. Anaerobic glycolysis also varied with age, but was the same in normal as in regenerating tissue.

The interesting observations of Mirski, that liver glycogen is decreased less by fasting in protein fed rats than after carbohydrate feeding, have been confirmed by Newburger & Brown (21). Ether anesthesia, however, produced an equal disappearance of glycogen in both groups. They conclude that there is no difference in the availability of the glycogen laid down from these two types of food, but suggest that carbohydrate metabolism is probably minimal in the protein-fed animals while those that have been consuming carbohydrate continue to metabolize glucose rapidly. The peculiar properties of isoleucine, which does not form glycogen but protects against insulin hypoglycemia, are also found by Lehninger (22) to apply to acetopyruvic acid; this substance is ketogenic in the fasting animal and leads to no deposition of glycogen, but will maintain the blood sugar level after injection of insulin. Conversion of these substances to glucose appears to be possible under emergency conditions. Fantl, Rome & Nelson (23) carried out *in vitro* observations on the enzyme system that forms glucose from glycogen and find that it has a sharp pH optimum at 6.6; the presence of glucose has little effect except at very high concentrations. They are of the opinion that pH may be a major factor in the control of glycogenolysis, and point out that the lack of effect of glucose does not favor Soskin's suggestion that the blood sugar level itself directly regulates glycogen synthesis and breakdown. It may be noted, however, that a great variety of

evidence indicates the relation of glycogenesis and glycogenolysis to blood sugar level under conditions where there is no apparent reason to suspect changes in pH. McBride (24) was not able to confirm previous reports that the accumulation of liver glycogen after a period of fasting is accompanied by the deposition of other liver solids, and shows that in the rat fasted thirty-six hours essential cell constituents and not storage materials are being lost by the liver. The role of the liver in the regulation of the blood sugar level is well discussed in a review by Drury (25). Deuel & Davis (26) have found that the blood sugar level is higher in rats with fatty livers than in normal animals, and the increase after oral glucose is greater (in females only).

As during the First World War, so in the last year attention to the problem of shock has been intensified by the needs of military medicine. Our knowledge of the part played by the liver in the formation of the plasma proteins, especially albumin, has stimulated interest in this phase of hepatic physiology in relation to the shock problem. The majority of articles on this subject are not suitable for inclusion in this review, however, since they do not contribute to our knowledge of liver function. One report that may be mentioned is that of Beattie & Collard (27), who were able to produce saturation of the protein stores of dogs by repeated plasma transfusions, further infusions of plasma resulting in a rise in plasma protein concentration. Plasma transfusions in hepatectomized dogs were followed by substantially as rapid removal of the administered protein as occurred in normal animals. Movement of protein into the plasma was also observed in the hepatectomized animals, under some circumstances. These authors then perfused isolated livers and found that protein was retained or added, depending on the original protein concentration of the perfusate. Post & Patek (28) found that when patients with cirrhosis, ascites, and reduced serum albumin concentrations were placed on high protein diets they remained in nitrogen balance, but there was little or no rise in the serum albumin. They conclude that in this type of liver damage food protein can be absorbed and retained but that albumin synthesis is impaired. These contributions appear to substantiate the view, previously expressed by various investigators, that the liver is important in the formation of the plasma proteins (especially the albumin) but is by no means the only tissue concerned.

Trowell (29) developed a new method for the perfusion of whole rat livers by which a constant rate of urea formation from the ammonia of the perfusate could be maintained over a four hour period. Adding ornithine to the perfusion fluid resulted in an increased output of urea, confirming the catalytic effect of this substance. The effect of arginine varied greatly from one preparation to another and these variations could not be correlated with the arginase concentration. Citrulline, glutamic acid, glutamine, and alanine had no catalytic effect, and citrulline was not converted into arginine or ornithine. They conclude that these results do not support either the ornithine cycle of Krebs or the amide-nitrogen cycle of Bach. Gornall & Hunter (30) used liver slices with a lactate substrate and ammonia as the only added source of nitrogen. They were able to confirm completely the observations of the Krebs school, and the accumulation of citrulline when ornithine was added led them to suggest that the conversion of citrulline to arginine is the limiting factor in the cycle. They have no explanation for the results obtained by Trowell in his perfusion experiments, except to suggest that the perfusion technique may not yet be satisfactory. Inhibition of arginase by an excess of ornithine is demonstrated by Bach & Williamson (31), who show that under these conditions the production of urea from added arginine is decreased. An excess of ornithine did not, however, decrease the formation of urea from ammonia, which leads the authors to the conclusion that arginine is not an essential intermediate in this process. A criticism of this method by Krebs (32) and a reply by Bach & Williamson do not resolve the differences between these two schools of thought.

The factors regulating the liver arginase concentration are further elucidated in two articles by Fraenkel-Conrat, Simpson & Evans (33, 34). They find that hypophysectomy is followed by a marked decrease in liver arginase which can be reversed by the administration of adrenocorticotrophic hormone, which also increases the arginase content in normal animals. Arginase is decreased by injections of growth hormone. Adrenalectomy produces a greater decrease in arginase than does hypophysectomy, while the administration of corticosterone, 11-dehydrocorticosterone, and 11-dehydro-17-hydroxycorticosterone (but not desoxycorticosterone) increase the arginase concentration. Pronounced changes in arginase concentration may result from dosages that do not

stimulate gluconeogenesis enough to maintain the carbohydrate stores of the body during fasting. The question of whether these changes are primary in the control of nitrogen metabolism or are secondary to other effects which may be produced is discussed. Smythe (35) has observed that rat liver slices, brei, or extracts will produce considerable amounts of hydrogen sulfide, and even elementary sulfur, from cysteine and cystine. The other principal products are pyruvic acid and ammonia. The hydrogen sulfide formation is greater under anaerobic than aerobic conditions, and the concentrations of the sulfur-containing amino acids used were quite high in comparison to those that might occur *in vivo*. Such experiments reveal the potentialities of tissues but it would be best to obtain confirmation by other methods, using the intact animal, before assuming that these potentialities are utilized under ordinary conditions; the author, in fact, does not permit himself such an assumption.

Because ketonemia usually appears under conditions which are associated with a low concentration of glycogen in the liver and a decreased blood glucose concentration, it has often been assumed (in the absence of any direct evidence) that ketogenesis is determined by the liver glycogen content. Somogyi (36) now reports that the blood acetone bodies definitely increase during alimentary hypoglycemia at a time when the liver is presumably well stocked with glycogen, and suggests that the rate of glycogenolysis principally determines whether or not the liver will liberate acetone bodies. Stark & Somogyi (37) followed the ratio of acetoacetic acid to β -hydroxybutyric acid in the plasma and the distribution of these substances between cells and plasma in the postabsorptive state and after glucose feeding. The intake of glucose causes β -hydroxybutyric acid to disappear more rapidly than acetoacetic acid, and the former may not be detectable while there are still significant amounts of the latter present in the plasma. Diffusion outward from the red cells appears to be slow, for as the acetone body level of the whole blood falls the concentration in the cells may come to be higher than that of the plasma. Deuel continues to present evidence which he interprets as favoring the ketolytic effect of carbohydrate. In these recent experiments Bobbitt & Deuel (38) showed that addition of glycogen to the substrate in which rat liver slices were bathed decreased acetone body formation and increased the rate of removal of butyric acid. The

mass of evidence now indicates quite clearly that an increase in the amount of available carbohydrate does not accelerate the utilization of the acetone bodies by the tissues but does depress the rate of acetone body liberation by the liver. It is of course possible that carbohydrate being available to the liver cells (although the availability of extracellular glycogen might be questioned) may accelerate ketolysis by this tissue, and in fact the opposite condition might account for the addition of acetone bodies to the blood when the supply of carbohydrate is low; it seems equally possible that it might favor an alternative pathway for butyric acid oxidation, an interpretation which is neglected by the author. Ennor (39) reports that livers which have been poisoned with carbon tetrachloride or phosphorus exhibit an increased oxygen consumption and an increased ketogenesis. In a later article (40) he states that the iodine number of the liver fatty acids is increased by carbon tetrachloride administration in the guinea pig but not in the rat, which fact he interprets as contradictory to Winter's evidence that hepatic poisons diminish the ability of the liver to desaturate fatty acids. Fishler, Entenman, Montgomery & Chaikoff (41) removed the livers from dogs and administered radioactive phosphorus. The recovery of P^{32} from the plasma phospholipids was greatly diminished as contrasted with normal animals, a fact suggesting that they are formed principally by the liver. The recovery of P^{32} containing phospholipid from kidney and small intestine, on the other hand, was not depressed; the lipid synthesized by these tissues would appear not to be available to the plasma. The phospholipid turnover in the liver is not affected by a deficiency of essential fatty acids, according to studies made by Barnes, Rusoff & Burr (42) using the determinable fatty acids from corn oil. Chaikoff, Eichorn, Connor & Entenman (43) produced cirrhotic changes in the livers of dogs by keeping the animals on high fat diets over long periods; they point out that this may have some bearing on the etiology of human cirrhosis.

VITAMIN A STORAGE, PRODUCTION OF DYSFUNCTION, AND OTHER TOPICS

Josephs (44) determined vitamin A in the plasma and in the liver under various conditions, and observed that when the vitamin A content of the liver is high the vitamin will not be as rapidly

removed from the blood during absorption as when its hepatic concentration is not elevated above the usual values. The vitamin A of the plasma remains at a relatively constant figure as the amount in the liver decreases, until when the liver concentration becomes very low the plasma level drops abruptly. It has been observed previously that the plasma vitamin A concentration in liver disease may be low in spite of an apparently adequate hepatic store. Popper, Steigmann & Dyniewicz (45) found that following carbon tetrachloride poisoning vitamin A is found in the damaged but not in the uninvolved areas, and that the former take up the vitamin more rapidly and release it more slowly. Stewart & Rourke (46) have studied the plasma vitamin A before and after surgery on patients with biliary tract disease with and without obstruction. When biliary tract obstruction was present the plasma vitamin A was usually insignificant even though the liver might contain large amounts, but the plasma concentration could be increased by long continued intramuscular administration of the vitamin. The plasma level tended to rise when the obstruction was relieved. Plasma carotenoids were substantially normal in all the patients observed. Abels, Gorham, Eberlin, Halter & Rhoads (47) gave dibenzanthracene to rats and observed a hepatic vitamin A depletion, but there were no suggestions of disturbance of liver function. They suggest that there may be competition between vitamin A and the dibenzanthracene for some hepatic protein.

Drill, Shaffer & Overman (48) have continued the observations of Drill & Hays on the effects of hyperthyroidism in dogs produced by thyroid feeding, with and without the inclusion of the vitamins of the B complex in the form of yeast, on liver function and on the behavior of other tissues. Most of the symptoms, including an abnormal retention of bromsulfalein, occur earlier during the course of thyroid feeding in the animals from which yeast is withheld. The elimination of the dye did not return to normal, even when a yeast concentrate was added to the diet, as long as thyroid was given. This substantiates the clinical evidence that hyperthyroidism involves an increased requirement for members of the B complex. Hough & Freeman (49) gave dogs a low protein diet, which resulted in hepatic injury as determined by an increase in the alkaline blood phosphatase and a decrease in rose Bengal clearance. Their previous reports on the protective action of protein and methionine in chloroform poisoning have been extended

by Miller & Whipple (50), who now report that methionine still protects even when given after the administration of chloroform, and that cysteine plus choline are likewise protective while choline alone is not. Rafsky & Newman (51) applied liver function tests in a series of patients of varying ages, and observed that abnormal results of the tests are frequent in individuals past sixty years of age.

Because it is known that several of the hormones are changed into relatively inactive forms by the liver, there has been continued interest in the fate of those that have not yet been completely studied. Mark (52) finds no indication that desoxycorticosterone is affected in any way by the liver; implantation of pellets of this hormone in the spleen was as effective as subcutaneous implantation. Leblond (53) considered that since pregnandiol seems to be the end product of progesterone metabolism in man it might escape further change, but actually he finds it conjugated by the liver; pregnandione was similarly affected. Insulin injected into the spleen or the liver itself was found by Mark & Lewis (54) to be as active as when given subcutaneously.

There has been previous clinical evidence that the formation of thrombocytes is depressed in the presence of hepatic cirrhosis. Morlock & Hall (55) have confirmed these observations, reporting that thrombocytopenia is present in 20 per cent of cirrhotics. It therefore appears that the effects of hepatic insufficiency upon the bone marrow encompass more than the well known disturbance of erythrocyte formation. Mann (56) has reviewed some aspects of the relation of the liver to other parts of the gastrointestinal tract. He quotes previously unpublished evidence on the streamline flow in the portal vein and distribution of blood from the various portal branches to separate lobes of the liver, and on an increase in portal venous pressure resulting from intestinal distension.

BILE

The Northwestern group have continued their observations on factors affecting the flow of bile. Warkentin, Huston, Preston & Ivy (57) distended the proximal colon in dogs and observed a reflex inhibition of bile flow in 70 per cent of the animals. This appears to be a celiac ganglion reflex since it is not interrupted by decentralization of the ganglion, but is abolished by nerve

section below the ganglion. Ivy, Annegers & Atkinson (58) and Ivy, Roback & Stein (59) carefully studied the effects of aloes and podophyllin (constituents of widely sold laxative preparations) on bile flow and on contraction of the gall bladder. No effect of these drugs was noted either on anesthetized or unanesthetized dogs, whether the bile was returned or was completely drained, or when the stools were made scybalous by feeding bone meal in order to simulate constipation. The effect of sodium dehydrocholate and desoxycholate were investigated by Cantarow & Wirts (60). Dehydrocholate in dogs with bile fistulas, but otherwise normal, brings about an increase in the concentration of serum bilirubin, a delay in the removal of bromsulfalein from the blood, and a decrease in the rate of bromsulfalein excretion in the bile. These effects were not observed after the administration of desoxycholate. Partial stasis in the biliary tract produced little change in the response to dehydrocholate, and this bile salt had no effect in animals previously treated with carbon tetrachloride. Wirts & Cantarow (61) compared the rate of disappearance of bromsulfalein from the blood with its excretion in the bile and conclude that a dual mechanism is probably involved; they suggest that the dye may be first removed from the plasma by the Kupfer cells and later secreted by the polygonal cells.

Cantarow and others (62) found that 90 to 95 per cent of the estrogenic activity could be recovered from the bile within 48 to 72 hours following the intravenous administration of 10,000 or 250,000 I.U. of estrone or 250,000 I.U. of alpha-estradiol to dogs. The form in which these hormones appeared in the bile was not identified. The rate of disappearance from the blood is more rapid than excretion in the bile, which leads the authors to suggest (neglecting the probability of diffusion into the body fluids as a whole) that these hormones must be stored in what they term the "biliary field." They correctly point out that biliary excretion rather than rapid hepatic conjugation may account for the inactivation by the liver, and indicate the possibility of an enterohepatic circulation of the estrogens. Having previously observed that the erythrocytes are more fragile in lipemic than in normal serum, Loewy, Freeman, Marchello & Johnson (63) studied the bilirubin output of bile fistula dogs and find it appreciably greater on high than on low fat diets which suggests increased red cell destruction. They entertain the possibility that during the absorp-

tion of fat a hemolytic substance is introduced into the circulation by way of the lymphatics. Ehrich (64) observed that the rate of excretion of cyanol and azofuchsin in the bile is dependent on the rate of renal excretion, being less when the latter is high; this calls to mind the similar interrelationship between biliary and urinary secretion that has been demonstrated for phenolsulfonphthalein.

The concentration of bile salts in specimens obtained by surgical biliary drainage was determined by Morrison & Swalm (65), using a stalagmometric method. In patients whose hepatic function appeared to be normal the bile salt content ranged from 1.6 to 3.0 gm. per 100 ml., with an average of 1.8, while in patients with liver disease the limits of variation were 0.38 to 2.25, and the average 0.74. In spite of severe signs and symptoms of biliary tract disease extending over as long as three years, the bile salt concentration could return to normal within three weeks after operation. Franke & Banda (66) analyzed duodenal contents for bile salts, using chemical methods, and found 74 to 414 mg. per 100 ml. before and 140 to 669 ml. after inducing evacuation of the gall bladder. The ratio of cholic to desoxycholic acid varied widely. Patients with gall bladder disease exhibited no abnormalities of bile salt concentration. It is probable that the methods available for such studies could be considerably improved, and future investigations of this type with better methods may well prove fruitful if further demonstrations of the depression of bile salt concentration by liver or biliary tract disease are presented. The bile is one of the least studied of the digestive secretions but is one of the most important, and the frequency with which deficiencies of the fat soluble vitamins (notably vitamin K) are seen and may be corrected by bile salt administration indicates that biliary secretion is more frequently inadequate than has been suspected until recent years.

A number of years ago Mellanby concluded that bile in the duodenum stimulated pancreatic secretion, and he believed the presence of bile to be a factor in maintaining the output of pancreatic juice. Thomas & Crider (67) have been unable to increase the secretion of the pancreas by the introduction of bile into the intestine, and they further find that bile diminishes the pancreatic response to peptone, soap, or hydrochloric acid; Mellanby's theory appears to be untenable. Whole bile or bile salts were placed in the stomach of the dog by Winfield & Kaulbersz (68). During the

resting phase hunger contractions were induced, while during motor activity the bile or bile salts usually produced inhibition of contractions.

Moore, Hellman & Jacobius (69) studied the effect of biliary obstruction in one member of pairs of parabiotic rats; there was no accumulation of bile pigment and therefore no jaundice but the bile ducts of the obstructed rat became filled with a clear secretion. The fibrosis, proliferation of the ducts, and necrosis occurred more rapidly in the parabiotic rat than after ligation in nonparabiotic animals, but the changes were eventually comparable. It seems evident that the secretions of the biliary tree can produce these effects when bile is absent from the duct system. The observations of Schmidt & Hughes (70) indicate that the principal fate of that fraction of the bile salts lost in the entero-hepatic circuit is destruction by the bacteria of the cecum; they could demonstrate but little destruction elsewhere in the gastrointestinal tract. Richter & Birmingham (71) observed that rats exhibit a diminished appetite for fats (self-selection diet) following ligation of the common bile duct.

In a brief communication, Okey (72) reports the accidental finding of gall stones in guinea pigs being used for the study of effects of high cholesterol diets. The stones occurred only when cholesterol and riboflavin were added to diets containing 25 per cent protein, and were not found when the riboflavin concentration was decreased. They were of the calcium phosphate type, containing some cholesterol. It may be hoped that this most interesting observation will lead to further investigations on the etiology of gall stones. Annegers, Snapp, Ivy & Atkinson (73) gave cincophen by mouth and found that its concentration in the bile is constant regardless of the size of the dose. When the bile was returned each hour the drug persisted in the biliary secretion for 16 to 24 hours, but as might be expected disappeared more rapidly if constant drainage was employed.

In spite of a careful perusal of the old and new literature dealing with the sphincter of Oddi, the reviewer is left with the impression that we still do not know the mechanisms by which this sphincter is controlled nor have we fully satisfactory information concerning how well its tone changes are coordinated with gall bladder contraction and relaxation. Bergh (74) has studied patients with cholecystectomy, choledochotomy, and intubation of the common

bile duct, and observed relaxation of the sphincter after the administration of egg yolk and cream while olive oil had little effect. Protein produced relaxation only once in four experiments and carbohydrate was totally inactive. In another article in which the literature is reviewed, Bergh (75) is led to question whether there is any nervous mechanism controlling the sphincter of Oddi in man. Kozoll & Necheles (76) find that sphincter of Oddi activity and duodenal motility are independent; intraduodenal saline (normal or hypertonic) frequently brought about sphincter spasm while glucose produced a moderate degree of contraction. These authors also report (77) that while the gall bladder and sphincter activities are usually coordinated, they appear at times not to act in concert. A number of agents, especially alkaline fluids, were capable of causing sphincter spasm; fats produced a temporary increase in tone followed by relaxation below the control level. Peristalsis in the common bile duct of man, visualized by Lipiodol, has been observed by MacDonald (78).

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GLOMERULAR FILTRATION, RENAL PLASMA FLOW, AND MAXIMAL RATE OF TUBULAR TRANSFER

The values of inulin clearance (C_{in}) for the measurement of glomerular filtration, of diodrast clearance (CD) at low plasma levels for the measurement of renal plasma flow, and of the maximal rate of tubular transfer (T_m) (excretion or reabsorption) expressed in milligrams per min., for the functional measurement of the mass of tubular tissue have been definitely established and widely used. Exogenous creatinine can be used also in practically all mammals with the exception of man as a measure of glomerular filtration. A new method for the measurement of creatinine in blood and urine using the photoelectric colorimeter has been devised (1).

Certain simplifications and improvements of technique have permitted the wider and easier application of these methods. A method for the colorimetric determination of inulin in blood and urine which does not require the preliminary removal of glucose from blood samples has been described (2), as well as simplified procedures for the determination of renal plasma flow and tubular excretory mass in human beings (3, 4). By collecting the urine during longer periods and injecting inulin and diodrast by subcutaneous route the following average data have been obtained in the normal rat: inulin clearance (C_{in}), 0.0027 cc. per gm. body weight per min.; diodrast clearance (CD), 0.0133 cc. per gm. per min.; T_mD , 0.00142 mg. per gm. per min.; CD/T_mD , 9.3 and C_{in}/CD , 0.20 (5). As Shannon (6) wisely states "these simplifying procedures will yield valid information only as their limitations are fully appreciated."

¹ This review should cover the period July 1, 1942 to June 30, 1943. Unfortunately due to restrictions imposed by war conditions many American and most of the European journals have not reached the reviewer.

The fundamental studies of Homer W. Smith and his collaborators have established that the renal blood flow (diodrast clearance) may vary widely in normal individuals, but that if the CD is correlated to the TmD, the variations of which are parallel, the results are fairly constant. For instance the isolated verification of a low CD does not permit the inference that renal ischemia is present; only if the TmD is normal or, better still, if the relation CD/TmD is lower than normal, such conclusion can be established.

The relation between inulin clearance and diodrast clearance, called the filtration fraction, permits an approximate evaluation of changes in the tonus of the glomerular arterioles. The mathematical treatment of the variables concerned has received further consideration. Improvements have been introduced into the equations for calculating the resistance of the afferent and efferent arterioles of the kidney to blood flow by taking into account also the viscosity and osmotic pressure of blood (7). The application of these formulae to data on the different renal function tests in the literature has permitted a series of conclusions regarding the mode of action of pitressin, atropine, renin, and angiotonin (hypertensin) on renal resistance, and the state of the renal arterioles in cases of essential hypertension and toxemia of pregnancy (8).

Hyperthermia induced by diathermy in dogs results in a decrease in plasma creatinine clearance and in urine flow due apparently to a decrease in renal plasma flow (9). Changes in environmental temperature did not alter the inulin clearance in normal or hypertensive subjects. In those which have a decreased inulin clearance, the renal plasma flow showed a slight decrease when in a hot environment and in two of six cases studied the diodrast Tm increased (10).

Rats exposed to low pressures reacted with polyuria, greater at lower temperatures, while the excretion of phenolsulphonephthalein was unchanged. To explain these changes an inhibition of the reabsorptive faculty of the tubular cells at low pressures (high altitudes) which would be increased by cold is assumed (11).

Shock due to the occlusion of limbs by tourniquets causes great decreases in diodrast and inulin clearances, filtration fraction, and urine volume; these changes are not associated with corresponding changes in blood pressure and are minimized if the col-

lection of fluid in the occluded limbs is prevented (12). In hypotension due to hemorrhage, renal blood flow and function parallel the blood pressure changes; transfusion restores both blood pressure and renal function and blood flow, but restoration is less adequate in successive hemorrhages due in part to renal vasoconstriction (13). Azotemia associated with gastrointestinal bleeding is apparently due to the decreased renal function with accompanying low blood pressure and dehydration (14).

In nephrotic children the elevated urea clearance observed is associated with an increase in both inulin and diodrast clearance, this fact indicating that it may be due to an increase in renal blood flow (15). On the other hand, in the uranium damaged kidney the diodrast clearance is reduced to the level of the apparent glomerular filtration as the result of the loss of the ability of the tubules to secrete diodrast (16). The interpretation of results of the renal function tests in the presence of kidney damage must be very cautious, taking into account the possibility of back diffusion of inulin and lower capacity of excretion of diodrast due to the tubular lesions. In the first case we could have an apparent reduction of glomerular filtration and in the second of renal blood flow.

In renal glycosuria the effective renal blood flow and the rate of glomerular filtration were found to be normal (17, 18). The tubular reabsorption of glucose at low blood sugar levels is lessened and the maximal rate of reabsorption may be normal (17) or lower than normal (18). In the latter case it was found that the TmD was also markedly decreased (18) showing the interdependence of the different tubular functions.

ENDOCRINE GLANDS AND KIDNEY

Neither the removal of the parathyroids nor the injection of parathyroid extract alter the clearance of phosphate by the kidneys in normal dogs (19). These results do not substantiate the contention that the primary effect of the parathyroids is to affect the ability of the kidney to excrete phosphate. Furthermore, experiments on rats show that complete nephrectomy does not prevent the action of the parathyroid hormone on bones (20).

Testosterone propionate not only hastens the compensatory hypertrophy of the kidney after nephrectomy in rats but causes

renal enlargement probably not mediated by the pituitary (21). Testosterone slightly increases (21) or does not affect (22) renal functions in dogs as measured by the inulin or creatinine and diodrast clearance tests. On the other hand, the administration of testosterone propionate causes the maximal capacity of the human kidney to excrete diodrast (Tm) to rise more rapidly during renal compensatory hypertrophy due to unilateral nephrectomy (21).

In the dog it causes also a striking increase in diodrast Tm which returns to normal after suspension of treatment. This increase in diodrast Tm without change in diodrast clearance would mean renal ischemia if it were due to tubular hypertrophy. It may be due simply to an increase in tubular function. In any case no rise in blood pressure was observed in the treated dogs (22). Large doses of methyltestosterone increase creatinuria in normal young men (23) and in some patients with Simmond's disease (24).

Overdosage of desoxycorticosterone acetate (25) or progesterone (26) causes nephrosclerosis, generalized tissue edema, and cardiovascular changes in the chick. High doses of sodium chloride added to the drinking water of chicks may suffice to elicit these changes (26). These findings may have some bearing on the relation between adrenal hyperfunction and hypertension, but further work is necessary along this line before this problem is clarified.

The survival time after nephrectomy or ureteral ligation in rats or dogs depends on the level attained by potassium in serum. If desoxycorticosterone or a low potassium diet is administered before nephrectomy or ureteral ligation, body potassium is depleted and the time of survival after operation is prolonged (27), but if desoxycorticosterone is administered after ureteral ligation no beneficial effect is obtained (28).

The hormonal control of water and electrolyte excretion.—The role of the endocrine system in the control of water and electrolyte transfer has been further studied. The physiological control of these processes is humoral in nature and new evidence has been presented that the absence of the renal nerve supply does not affect them (29).

The hormones of the adrenal cortex enhance the ability of the tubule to reabsorb sodium and chloride. Among the adrenal cortical compounds having this effect are 11-desoxycorticosterone,

corticosterone, and dehydrocorticosterone; the addition of an hydroxyl group on C₁₇ reduces the "sodium and chloride retaining" potency of desoxycorticosterone (30). Désoxycorticosterone produces polyuria in normal dogs (31) and rats (32) apparently by decreasing the concentration power of the kidney (31) and increases the existing polyuria of dogs and rats with diabetes insipidus (31, 32) but fails to have this action in the cat (33) or in hypophysectomized rats (32). The decreased renal excretion of chlorine in rabbits following the administration of desoxycorticosterone has been attributed to a diminished glomerular filtration (34).

The glandular hypophysis also exercises a humoral influence on the kidney functions. Removal of the anterior lobe or of both lobes of the hypophysis in rats causes a decrease in rate and extent of water diuresis (35). Diodrast and inulin plasma clearances and diodrast Tm are markedly decreased by loss of the anterior lobe of the hypophysis in dogs but diodrast and inulin extractions at low plasma levels are unchanged. In dogs with intact anterior lobe in which the tissues where the antidiuretic hormone is formed are functionless, these renal functions are unaffected (36). It is probable that the eosinophil cells of the anterior hypophysis are responsible for the influence of this gland on the kidney because, while patients with acromegaly show increased values of urea clearance, those with Cushing's syndrome show normal inulin and diodrast clearances (37).

Thyroidectomy decreases and thyroid feeding increases considerably the polyuria of cats with diabetes insipidus (38) but not of hypophysectomized rats (39). In dogs with latent polyuria due to partial destruction of the pars nervosa of the hypophysis, thyroid feeding produces an enormous increase in urine flow which is at least partly due to diminished reabsorption of water. It appears probable that thyroid interferes with the action of the antidiuretic hormone on the renal tubules (40).

Antidiuretic hormone.—The antidiuretic hormone of the posterior pituitary has probably a dual role: it has a depressing action on the reabsorption of sodium and chloride, and it enhances water reabsorption.

By infusing intravenously saline solutions of different concentrations and calculating the ratio of concentration of chloride in the tubular reabsorbate to that in plasma (R/P ratio) one can

obtain some idea of the relative chloride and water filtration and reabsorption. This R/P ratio is lowered by the infusion of hypertonic salt solution, is found elevated in dogs with diabetes insipidus, is lowered by the administration of pitressin which also returns to normal the elevated R/P ratio that results from the infusion of hypotonic salt solution. From these studies it is suggested that the neurohypophysis regulates the partition of water and chloride between tubular reabsorbate and urine (41) and that the effect of hypotonic or hypertonic salt solutions is to inhibit and increase respectively the liberation of antidiuretic hormone (42). By changing the state of hydration the factors determining the excretion of water and electrolyte in dogs with diabetes insipidus have been studied. The more important factors appear to be

the volume of extracellular fluid and plasma and the concentration of the contained electrolyte, glomerular filtration rate and the excretion of electrolyte, urea and water itself as well as the tonicity of the urine (43).

Similar studies in patients with diabetes insipidus have shown that low salt intake decreases the water resorptive power of the tubule, while high salt intake, estrogens, and posterior pituitary extract increase it. The capacity of the tubule for reabsorption of salt is increased by estrogens and desoxycorticosterone acetate (44). The variable effects of pregnancy upon the course of diabetes insipidus in women depends probably on which hormonal influences predominate (45, 46).

In patients with diabetes insipidus, inulin clearance and diodrast Tm did not change in the antidiuretic phase induced by the injection of pituitary extract, while the diodrast clearance during the diuretic phase was 20 to 60 per cent below that during anti-diuresis (47).

Posterior pituitary extract injected into frogs retains progressively more of the water administered until a maximal effect is reached after which, if further water is given, the water retaining effect of the extract decreases rapidly (48). The effect of posterior pituitary extracts on the water uptake of frogs is lower than in normal after removal of anterior or posterior lobe or both and infundibular lesions (49).

The injection of posterior pituitary hormone inhibits the diure-

sis normally produced in men by the ingestion of one liter of water. This test which has been called by Pasqualini *et al.* "enforced tubular reabsorption" has been applied to patients with acute nephritis in which the antidiuretic effect of pitressin was found to be greatly reduced (50, 51). The increase in the specific gravity of the urine after the injection of pitressin has also been adopted as a test of renal function (52, 53).

Pitressin tannate in oil seems to be the safest and most effective slow acting preparation yet available for the treatment of diabetes insipidus (54).

The injection of pitressin produced the disappearance of the sensation of intense thirst in twenty minutes in patients with diabetes insipidus who had been deprived of water for many hours. This suggests that apart from its action upon the kidneys the antidiuretic hormone may act upon other tissues, perhaps on the central receptors of thirst (55).

No correlation could be found between the cytology of the pars nervosa of the hypophysis and variations in the state of hydration in rats (56).

The quantity of hormone liberated by the posterior lobe of the pituitary has been estimated by indirect methods. Assay of the quantity of hormone liberated in response to short-lived emotional stress during water diuresis shows this to be of the order of a few milliunits. As one milliunit was sufficient to reduce the urine flow during water diuresis to the resting level it is presumed that under physiological conditions amounts of about this order circulate in the peripheral blood (57). This is in agreement with the observation that one to five milliunits (pressor) of antidiuretic hormone per hour by constant intravenous injection produced graded antidiuresis in hydrated dogs (15 kg.) with diabetes insipidus (58). By comparing the amount of hormone liberated before and after removal of the posterior lobe it is concluded that only about 5 per cent of the antidiuretic function of the neurohypophysis remains when the posterior lobe has been removed (57).

The amount of antidiuretic substances excreted in the urine by dogs with experimental renal hypertension during normal hydration or during dehydration was the same as that of normal dogs (59). The origin of this substance is still questioned: differences are described between it and pituitrin. It can appear in the

urine of normal persons, it is found in large amounts in the urine from patients with toxemia of pregnancy, and the placentas of these patients contain larger quantities of antidiuretic substance than placentas from normal women (60).

Small doses of the oxytocic hormone of the pituitary gland exert a strong diuretic action and decrease urinary phosphorus excretion. The possibility that these actions may be of physiological significance in maintaining water balance must be considered (61).

MISCELLANEOUS

An examination of the equation which gives the amount of osmotic work necessary for the formation of urine has been accomplished in order to determine the amounts of excretory water and solids which will give the least work, and the effect on osmotic work of changes in blood concentrations (62).

Clearance studies of sulphate (63), potassium (64), and phosphate (65, 66) show that their excretion depends on their serum concentration and filtration rate, but are more or less independent of the associated ions. The intravenous injection of neutral potassium sulphate is followed by a marked increase in sodium excretion (66). The demonstrations that the tubular reabsorption of sulphate and inorganic phosphate are limited by a maximal rate have not received confirmation, (63, 65).

The urea clearance is lower in premature than in full term infants, and in both groups of young infants it is lower than that reported for older subjects. This is related to lower glomerular filtration rates rather than to increased tubular reabsorption of urea (67).

The diuretic action of alcohol has been studied on man. The diuretic following an alcoholic drink is roughly proportional to the amount of alcohol present when volume and other constituents are maintained constant, and is dependent mainly on the duration of the increasing blood alcohol concentration. Variations in external temperature may affect this relationship, diuresis being higher at a lower temperature (68).

The effect of the volume of urine excreted on the amount of hippuric acid eliminated has been studied and a direct relation found between them (69).

Only part of the nicotine absorbed by tobacco smokers is excreted as such in the urine, the amount excreted being greater when the urine is acid (70); about 10 per cent of the nicotine given by subcutaneous injection to the dog is excreted unchanged in the urine (71).

Arsenic is excreted in humans and probably in most animals almost entirely via the kidneys (72).

The renal excretion of cyanol and azofuchsin I is independent of their hepatic excretion except in cases in which the liver is severely damaged. Thus the use of dyes as a measure of renal function is only vitiated when the liver is severely damaged (73).

Studies of the clearance of hemoglobin have suggested that hemoglobin, like glucose, is filtered in the glomerulus and reabsorbed by the tubules and that this reabsorption mechanism is limited by a maximal rate of transfer. When this limit is surpassed hemoglobin appears in the urine. Dock's suggestion of a similar mechanism for proteinuria is based on experiments which show the presence of protein in the glomerular filtrate of kidneys perfused with ice cold serum, and the staining of the proximal convoluted tubules when dyes are injected intraperitoneally in rats with severe proteinuria (74).

Renal lymph collected in the capsular lymphatic trunks comes from the cortex and that collected in the hilar trunks from the medulla. Renal lymph contains more urea than the renal arterial or venous blood. By comparative studies of the glucose and inulin content of renal and cervical lymph the conclusion is reached that renal lymph is derived apparently from both the renal blood plasma and the tubular reabsorbed fluid. (75, 76).

ANATOMICAL AND PATHOLOGICAL STUDIES

Fluorescent granules are sometimes found at the glomerular pole of human kidney but they are absent in normal animals and in dogs with experimental hypertension (77).

The renal lesions produced in the albino rat by diets deficient in choline have been studied as well as the processes of repair which, occurring after the initial acute congestive phase, lead to nearly complete recovery (78). These lesions have been attributed to a lack of labile methyl groups or to a failure of phospholipid formation in the liver (79).

Trypan blue, injected subcutaneously, is more heavily deposited in the proximal convoluted cells of the kidney in guinea pigs deficient in vitamin C than in normal. This is interpreted as indicating a pathologic change in these cells as a result of the vitamin-C deficiency (80). It would be interesting to know which if any of the renal function tests are altered in this condition.

The injection of mercuric chloride to mammals and frogs affects almost exclusively the proximal convoluted tubules of the kidney with necrosis of its cells. The lesions affect principally the second and third quarters of the convoluted tubule, the initial, and especially the terminal, portions being rarely damaged (81).

The long continued administration of alkali in man with or without alkalosis does not lead to significant anatomic changes in the kidneys (82, 83).

The intravenous injection of a solution of sucrose produces maximal diuresis (90 to 100 per cent elimination of the fluid injected in the rabbit and 80 per cent in the dog). As the histological and functional changes which occur in the kidney disappear in a short period and the kidney seems to adapt itself to the action of further injections the authors feel confident that this procedure can be applied safely to humans whenever high urine volumes are desirable (84, 85). Studies on the nephrotoxic nephritis produced in rabbits by the injection of nephrotoxic duck serum suggest a mechanism different from that generally accepted (86). In rats with severe acute nephritis induced by anti-kidney serum significant hyperlipemia is regularly encountered (87). The same occurs in dogs after nephrectomy or renal injury caused by administration of mercury bichloride, uranium nitrate, or potassium bichromate (88). The mechanism by which the kidneys influence the blood lipids is still unknown.

The syndrome observed following prolonged compression beneath debris has been thought, on clinical grounds, to be the result of muscular necrosis. In rabbits, which have practically no myohemoglobin, myohemoglobinuria and renal failure did not occur after crushing the limbs (89). In dogs, whose muscles contain myohemoglobin, the renal failure occurred (90). The possibility that the renal failure observed in this syndrome may be caused by the excretion of myoglobin has been strengthened by the observations that injection of myoglobin into rabbits with induced acidosis produced death from renal failure (91). But Bing (92) could not

confirm this effect in dogs. The injection of crystalline methemoglobin and not of metmyoglobin or hemoglobin into dogs with induced acidosis was followed by a fall in glomerular filtration and renal plasma flow, and by the development of renal lesions similar to those found in patients with crush syndrome, and in some cases by death in uremia (92).

Porphyrinuria is a frequent finding in the aged individuals (93) and the administration of nicotinic acid results in its disappearance (94).

A review of modern opinions on the mechanisms responsible for the formation of urinary calculus and a method for their classification have appeared (95). Mechanical shaking and the exposition to exhaust gases led to the formation of urinary calculi in rats (96). The changes responsible for the appearance of these calculi have not yet been studied.

Hematuria and anuria have been frequently reported following the use of sulphonamide therapy (97 to 104). It results from the deposition of crystals of the acetylated compounds in the renal tract. Concentrated urines, low temperatures, and acidity favour this deposition. The administration of fluids and alkalis (105 to 108) and rise in temperature (108) will prevent it. For the treatment of anuria early ureteric catheterisation and lavage (98, 99), massage *per rectum* of the kidneys and accessible parts of the ureters (101), and surgical intervention have been advocated. Apart from this mechanical obstruction there may be toxic effects on the tubular epithelium (100, 103, 109) similar to those caused by mercuric bichloride.

EXPERIMENTAL RENAL HYPERTENSION

During the past year many contributions have been made in this field of investigation, and a fair number of general reviews on the subject have appeared (110 to 113).

Induction of hypertension.—Hypertension produced by constriction of the renal artery in sheep and goats (114) is similar to that of the dog. Notwithstanding the lack of confirmation by other careful workers it is maintained that the repeated temporary complete closure of the renal pedicle in the dog produces, in exceptional cases, permanent hypertension (115). Hypertension produced in rats by enveloping the kidney in silk, cotton batiste, or collodion has been further studied (116, 117, 118). The systolic blood pres-

sure of rats with hypertension due to constriction of one renal artery is sharply reduced during the latter part of pregnancy and rises again after delivery (119). Adrenalectomy produces an abrupt and marked decrease in the blood pressure of hypertensive rats, which can be only partially corrected by desoxycorticosterone (116). Grollman & Rule (120) joined rats in parabiotic union: hypertension induced by perinephritis in one member was or was not transmitted to the intact co-twin. The authors consider these findings as consistent with the view that the kidney elaborates a substance in the absence of which hypertension results. But in the reviewer's opinion they are also in favour of the action of a pressor agent liberated by the ischemic kidney which, depending on the amount released and the rapidity with which the tissues will destroy or remove it, will be able or not to cause hypertension in the intact co-twin.

Daily intramuscular injections of diethylstilbestrol into normal rats produced a gradual rise in blood pressure reaching hypertensive levels in many cases (121). This response may be due to the attendant hypertrophy of the adrenals or to an action upon the kidney which may be altered by sterols (122). The hypertensive effect of the administration of desoxycorticosterone on rats has been confirmed, but no increase in blood pressure was obtained by the oral administration of large doses of vitamin D₂ (123).

Dietary deficiency of only the heat-stable fractions of the vitamin B complex produces in rats a significant and persistent rise in blood pressure which can be reversed on restoring this factor to the diet (124). These findings seem to show that some types of hypertension may be metabolic in origin, the cause being perhaps a diminished oxidative activity of the kidney.

The influence of experimental hydronephrosis on the blood pressure has been studied on dogs. Complete ureteral occlusion is followed by a rise in blood pressure which persists until the animals die in uremia. Partial ureteral occlusion is followed by a transient elevation, but addition of unilateral hydronephrosis to contralateral renal ischemia intensifies the hypertension (125).

HUMORAL MECHANISM

Since Page and co-workers and Braun-Menendez, Fasciolo, Leloir & Muñoz discovered simultaneously and independently the substance causing renal hypertension formed by the interaction

of renin and blood, much work has been done on this aspect of the problem. Braun-Menendez, Fasciolo, Leloir & Muñoz in successive papers showed that renin which was released by the ischemic kidney acted enzymatically upon a serum globulin (hypertensinogen or hypertensin precursor) giving rise to the formation of a vasoconstrictor substance (hypertensin) which caused a rise in blood pressure. Hypertensin was found to be destroyed by a substance present in blood and tissues which was named hypertensinase. Page and collaborators after many hesitations have admitted the enzymatic nature of this reaction (126) but they call renin activator the substrate upon which renin acts, angiotonin the product of the reaction and, recently, angiotonase the substance which destroys it. This problem in terminology is considered by Lewis & Goldblatt (112) who, in a splendid review on the subject, write:

If it is eventually proved that the resultant product of the interaction of these two substances (renin and its substrate) is the cause of the elevated blood pressure, then the specific term "hypertensin" of the South Americans will be more pertinent than the non-specific term "angiotonin." However until the substance in question is actually isolated from the systemic circulation of patients with essential hypertension and/or animals with experimental renal hypertension, it is well to continue to use both terminologies side by side, but to bring them in line we suggest the terms "pre angiotonin" for renin activator and "pre hypertensin" for hypertensin precursor.

Renin has been found already in the systemic blood in many cases of human (127) or experimental hypertension (128). But it must be admitted that further work is necessary to prove conclusively that this substance is the only one responsible for the elevated blood pressure.

Renin.—Injections of renin into the maternal bloodstream of pregnant rats does not affect the fetal blood pressure, and, if the dose is larger, it causes a profound fall similar to that produced by the injections of angiotonin (hypertensin) or epinephrine (129). Apparently renin is too big a molecule to pass across the placenta.

New studies have appeared on the sensitivity of unanesthetized dogs to the pressor action of renin. It has been found that dogs recently nephrectomized usually react normally to renin although in certain instances the pressor effect is greater and lasts longer than in the normal controls (130). In dogs with bilateral experimental renal abnormalities or with uremia, the pressor effect of multiple doses or continuous injection of renin was more pro-

longed than in the normal controls (131). Dogs nephrectomized forty-eight hours previously were hypersensitive to renin and the pressor effect was usually markedly prolonged (130). Just which are the factors which account for the hypersensitivity to, and the prolonged action of, renin in dogs with renal abnormalities has not yet been determined. This point merits a thorough study. The increase in hypertensinogen (prehypertensin) and the lesser destruction of renin in nephrectomized uremic dogs which have been reported are possibly not the sole factors.

Hypophysectomized dogs react normally to renin (130) but adrenalectomy produces in many instances a reduced sensitivity to renin while the sensitivity to hypertensin remains normal (130). This circumstance has been found to be associated with a fall in the concentration of hypertensinogen (pre-hypertensin) in the plasma (130, 112).

Repeated doses of hog renin to dogs lead to anaphylatic reactions and produce cardiac and gastrointestinal hemorrhages and necrosis in dogs with abnormal renal circulation (132). The pathological lesions of experimental malignant hypertension can be induced or accelerated by the injection of foreign renin (131).

Another method for the bioassay of renin has been presented (133). It was found that the response of normal unanesthetized dogs to renin is independent of the body weight of dogs weighing between 10 and 25 kg. A dog-unit of renin is defined as the "amount which raises the blood pressure at least 30 and not more than 35 mm. Hg within 3 min. in at least 3 unanesthetized dogs" (133).

This represents some advantage when compared with similar methods which use the rise of blood pressure produced by renin as a test. But the *in vitro* methods (direct or indirect) described by Leloir *et al.* (134) which measure respectively the hypertensin formed or the hypertensinogen which disappears after incubating renin and hypertensinogen are undoubtedly much more sensitive and quantitative. A modification of the indirect method of Leloir *et al.* has been devised for the determination of human renin. It is based on the fact that while human renin acts on both human and bovine hypertensinogen, pig's renin acts on bovine hypertensinogen but not on human. The human blood containing renin is incubated with a measured amount (about one unit) of bovine hy-

pertensinogen in the presence of hypertensinase. At the end of the incubation period (six hours) an excess of pig's renin is added in order to measure the bovine hypertensinogen which remains. By comparing with a control, the amount of hypertensinogen transformed by the action of human renin can be calculated (135).

Because of the important role played by renin in the development of experimental hypertension a study was made of the mechanism by which renin injected intravenously disappears from the blood (136). The solution of hog renin used contained approximately 100 units per cc., one unit of renin being the amount which, when incubated for two hours at 37°C. with hypertensinase-free hypertensinogen, gives rise to the formation of 0.5 unit of hypertensin (137). After the intravenous injection of 2 to 3 cc. of this solution into normal dogs the renin disappears from the blood usually within thirty minutes. In dogs recently nephrectomized renin disappears from the blood in one to three hours. The same delay is observed in nephrectomized and hepatectomized and in eviscerated dogs. In uremic dogs the injected renin disappears slowly from the blood. It is concluded that although the kidney seems to have some destructive action, destruction of renin by the tissues is the principal factor in its disappearance from the blood and that this destructive action is altered in uremia. The excretion of renin by the kidney does not seem to be an important mechanism since only when the amount of renin injected exceeded 2 cc., was a fraction of it found in the urine. No neutralizing or destructive property against renin was demonstrable in blood from normal dogs. The mechanism by which the kidney and the body tissues destroy renin remains to be demonstrated.

In the forementioned study an increase in the concentration of renin in the blood was observed in one anesthetized control dog which presented a picture of shock. In view of this observation which suggested that in shock the kidney might liberate renin, a systematic study of the secretion of renin by the intact kidney was made (138). Profound lowering of the blood pressure by hemorrhage or shock causes the liberation of renin by the intact kidney of normal anesthetized dogs, renin being detected in the systemic blood. Even short periods (four to eleven minutes) of profound arterial hypotension produce the same effect. It can be concluded that, whenever the blood pressure decreases, the normal kidney

secretes renin which through the formation of hypertensin will tend to restore normal blood pressure. The inference is drawn that the kidney participates in the regulation of arterial blood pressure although it is not essential for its maintenance. No renin could be detected in the blood of nephrectomized dogs after hemorrhage or in normal dogs intoxicated with potassium cyanide or subjected to respiration of mixtures poor in oxygen. This raises the question of what is the stimulus for the formation of renin. As anoxemia and histotoxic anoxia were not followed by the presence of detectable amounts of renin, it appears that anoxia may not be the cause of the liberation of renin by the ischemic kidney. But anoxia does not prevent the secretion of renin by the kidney when the systemic blood pressure is lowered (138). Sodium cyanide also did not prevent the formation of renin by the completely ischemic kidney (139). Here is another of the fundamental problems which should be thoroughly studied. The idea that a diminished pulse pressure within the kidney causes the liberation of renin has no solid experimental proof.

The site of renin formation in the kidney has been the object of new studies (140, 141). The specific necrosis of proximal convoluted tubules produced by the administration of tartrate to adult rabbits deprived the kidneys of these animals of renin, a fact indicating that the epithelium of the proximal convoluted tubules is concerned in the formation or storage of renin (140). In the developing hog fetus the mesonephros undergoes progressive degeneration and terminal metaplasia whereas the metanephros increases in size and development. In the former, in fetus between 7 and 100 mm. in length, the tubules degenerate while the glomeruli remain unchanged and the amount of renin diminishes as the length of the fetus increases. In the metanephros the tubules are at first poorly developed in relation to the glomeruli but, as the fetus grows, the development of the proximal convoluted tubules accounts for most of the growth of the kidney. The concentration of renin in the metanephros increases with the age of the fetus. It is apparent that the amount of renin is related to the number and size of the tubular components of the kidney and is independent of its arterioglomerular component. No evidence was found in either type of kidney of juxtaglomerular cells (141) as described by Goormaghtigh who suggested that the afibrillar cells in the wall

of the afferent arteriole produce a pressor substance. Two articles on this anatomical formation and its possible relation to hypertension have appeared (142, 143) but the results above reported seem to discard the juxtaglomerular complex as the site of formation of renin.

The detailed results of a study previously reported on the specificity of the renin-hypertensinogen reaction in a variety of different species have been published (144). Renin extracted from kidneys of mammals reacts to form hypertensin with hypertensinogen from any mammal with the exception of man. Human renin is active on the hypertensinogen of every mammal including man. Renin is found in the kidney of chicken and duck and it reacts with hypertensinogen from any of those birds but not with mammalian hypertensinogen nor is mammalian renin active on bird plasma. There seems to be no renin in the kidneys of toads and shark.

Hypertensin showed no specificity; the product of the reaction between mammalian renin and hypertensinogen showed its characteristic pressor action on dog, chicken, toad, and snake. Dog and chicken do not show tachyphylaxis to repeated injections of hypertensin while toad and snake are rapidly rendered tachyphylactic. This difference has been found to be associated with a prolongation of the pressor action of hypertensin in the poikilotherms which results from the retardation of the destructive action of hypertensinase by the low body temperature of these animals (144).

Hypertensinogen (pre-hypertensin, pre-angiotonin).—Hypertensinogen, the substrate in blood serum upon which renin acts, was found to be a globulin. Different globulin fractions obtained by ammonium sulphate precipitation of hog's serum were analyzed electrophoretically and incubated with renin. The formation of angiotonin (hypertensin) was found to be proportional to the amount of α_2 -globulin present (145).

That hypertensinogen is originated in the liver has been confirmed (146) but no diminution in the concentration of hypertensinogen in blood plasma was observed after hepatectomy if the kidneys were also removed (146). This seems to show that the cause of the disappearance of hypertensinogen from plasma following hepatectomy (147) or destruction of the liver (147, 112) was the liberation of renin by the kidneys due to the fall in blood pressure.

Hypertensinogen decreases and even disappears from the systemic blood of untreated adrenalectomized dogs (112, 130). Before attributing to the adrenals an influence in the formation of hypertensinogen it would be wise to eliminate the possibility that the low blood pressure of untreated adrenalectomized dogs, through the liberation of renin by the kidney (138), is not the cause of the disappearance of hypertensinogen from the blood. In fact it has been shown that in hemorrhagic shock plasma hypertensinogen decreases in intact or adrenalectomized dogs and not in adrenalectomized-nephrectomized dogs (148).

The hypertensinogen concentration of the plasma of patients with various diseases has been studied (149). It was found essentially normal in hypertension, renal insufficiency, anesthesia, and various other conditions including one case of Addison's disease, but often significantly decreased in hepatic insufficiency.

Hypertensin (angiotonin).—It was found that effective renal blood flow and arterial pressure decrease during the syncope of orthostatic hypotension. Injection of angiotonin (hypertensin) at this time increases renal blood flow and blood pressure and relieves syncope (150). Injection of angiotonin (hypertensin) in six normal persons caused a decreased stroke volume and cardiac output as measured by the ballisto-cardiograph (151).

The blood pressure of the fetal rat is lowered or unchanged when a pressor dose of angiotonin (hypertensin) or epinephrine is injected into the maternal circulation (129).

Hypophysectomy, recent bilateral nephrectomy, and bilateral adrenalectomy cause no change in the sensitivity of dogs to the pressor action of hypertensin (angiotonin) or epinephrine. Dogs nephrectomized forty-eight hours previously are frequently hypersensitive to hypertensin and epinephrine (130).

Hypertensinase.—Experiments have been reported which seem to show that blood from an acutely ischemic kidney has a lesser concentration of hypertensinase than normal blood (152), which would mean that the ischemic kidney produces less hypertensinase. But Dexter (153) who made very careful quantitative determinations found between 1.5 and 3.9 units of hypertensinase per cc. of plasma in normal dogs. The hypertensinase content of plasma of dogs nephrectomized forty-eight hours previously and of dogs rendered hypertensive by renal ischemia was found normal.

Page and co-workers (154) believe that the antipressor effect

of their kidney extracts may be due to the hypertensinase they contain. They call angiotonase this angiotonin destroying activity of kidney extracts and consider it also an enzyme. The method used to assay the angiotonase (hypertensinase) activity is very similar to that already described by Fasciolo *et al.* (155). They have found two angiotonases in their kidney extracts with optimum activity at pH 4 and 7.5 respectively.

An aminopeptidase enzyme obtained from yeast inactivates both hypertensin and pepsitensin; the hypertensinase activity of renal extracts may also be attributed to the aminopeptidase enzyme contained in kidney tissue (156).

Pepsitensin.—By the action of pepsin on hypertensinogen a vasoconstrictor and pressor substance is formed which has been named pepsitensin. A comparative study of this substance and hypertensin has shown great similarity in their chemical and pharmacological characteristics (157). Nevertheless recent work has shown that though both substances proceed apparently from the same substrate in the blood they present at least one difference, i. e., hypertensinase of red blood cells which rapidly destroys hypertensin does not affect pepsitensin (158).

TREATMENT OF HYPERTENSION

Many lines of investigation, some of them new, have been followed during the past year in the attempt to arrive at a specific treatment of arterial hypertension. An excellent review has been written by Goldblatt *et al.* (110). New reports on the effects of the administration of kidney extracts to hypertensive patients have appeared (154, 159). The results are still encouraging but while some authors suggest a relation between the antipressor activity and the angiotonase (hypertensinase) activity of their extracts (154), others have shown that the decrease in arterial pressure can be obtained also by kidney extracts poor in hypertensinase (159). This seems to show that the action of these extracts is nonspecific. The occurrence of pyrogenic (160) and local tissue (154) reactions and perhaps also of general reactions allergic in nature (159) may be the cause of the fall in blood pressure. The important work of Chasis, Goldring & Smith (160) shows that blood pressure can be reduced in hypertensive subjects by the intravenous administration of pyrogenic material such as pyrogenic inulin, typhoid vaccine, and tyrosinase. This effect can be obtained

without a rise in body temperature by premedication with amidopyrine. The fall in blood pressure appears to be due to an asthenic action on the cardiovascular system. The final words of this article read thus: "Whenever the blood pressure of a hypertensive subject is reduced by the parenteral administration of a foreign organic material, this pyrogenic type of response should be excluded before a specific hypotensive property is attributed to the agent used. And any pyrogenic material should be administered cautiously, since it may induce an alarming degree of peripheral circulatory failure, as illustrated by one of our subjects." Renal irritation from the use of foreign protein therapy has also been reported (161).

The daily intramuscular injections for many months of partially purified hog renal extract containing renin is claimed to produce a lowering of the blood pressure of dogs with renal (162, 163), or spontaneous (164) hypertension, and to prevent the development of hypertension due to renal ischemia (162, 165). Simultaneously, antirenin—a substance which neutralizes *in vitro* the pressor action of renin—is formed and is demonstrated in the serum (or plasma) of the treated animals (166). It is not yet established that the development of antirenin is the cause of the prophylactic or antipressor effect of the injections of renin (162, 165). Friedman *et al.* (167) have been unable to confirm the blood pressure reducing properties of renin, crude or purified, nor the constant development of antirenin. Antirenin developed by the repeated injections of heterologous renin shows considerable crossing of neutralizing properties. For instance serums of dogs injected with hog renin neutralized the pressor action of hog, dog, rabbit, and cat but not of human renin. Human antirenin appears specific for human renin (166).

The antipressor effect of tyrosinase previously believed to be due to its enzymatic action presumably upon the renin-hypertensin system, has been shown to be nonspecific. The injection of heat-inactivated tyrosinase preparations lower the blood pressure of hypertensive subjects as effectively as the enzymatically active preparations (168).

The effectiveness of large doses of ascorbic acid in lowering the blood pressure of patients with essential hypertension is reported (169). However the difficulty in appreciating clinically the hypotensive properties of various remedies in essential hypertension has been emphasized (170).

Large doses of vitamin-A concentrate by mouth lower the blood pressure of hypertensive dogs (171) and rats (172, 173), but, as highly purified vitamin A was ineffective (174), and preparations in which vitamin A was previously destroyed by heating (175), ultraviolet irradiation, or oxidation (172) were equally or even more effective, the depressor activity of these preparations is obviously not due to the presence of vitamin A. Fish body and liver oils contain this blood pressure reducing substance and are made more active by oxidative procedures (173, 172). The nature of this substance and its mechanism of action are still unknown.

The work of Bing and co-workers (175a) has provided a basis for the hypothesis that hypertension which results from renal ischemia may be due to the faulty deamination of certain aminoacids in the kidney. The aromatic aminoacids would be as usually decarboxylated to form amines with pressor properties but deamination of the latter would not occur due to anoxia. In favour of this hypothesis it has been reported that the intravenous injection of *l*-dihydroxyphenylalanine produces a marked rise in blood pressure of cats with experimental hypertension, and men with essential hypertension while no rise is produced in normal cats and a less marked one in humans with normal blood pressure (176).

It has been attempted to counteract the pressor amines which according to this hypothesis would accumulate in the blood, by the introduction into the body of chemical compounds designed to inactivate and destroy them. Adrenochrome derivatives given intravenously (177) and three paraquinones and one diortoquinone (178) given by oral or subcutaneous route were found to reduce the blood pressure of hypertensive rats without giving rise to toxic manifestations or fever. These substances do not affect the blood pressure of normal rats.

HUMAN HYPERTENSION

The idea that the concepts derived from studies of experimental renal hypertension can be applied to the explanation of human hypertension continues to receive support from various sources. It is highly probable that essential hypertension may be the result of a number of factors (179, 180) but renal ischemia is perhaps the most frequent (181). The frequent association of adrenal tumors and hypertension has been observed (182).

The relation of urologic disease or abnormalities to hypertension has been the object of many studies (183 to 191) and new cases of elevation of blood pressure associated with renal ischemia have been reported (192 to 195).

In contrast to the finding of marked arteriolar sclerosis almost invariably in the histological sections of kidneys of hypertensive patients observed *post mortem* (196), in 53 of 100 renal biopsies from hypertensive subjects there was no or only mild vascular disease (182). These important observations of Castleman & Smithwick open the question of whether the renal arteriolar lesions are the cause or the consequence of arterial hypertension. Furthermore a significant correlation was found between the aspect of these renal biopsies and renal clearance determinations (197). The more severe the renal vascular disease the more reduced were the glomerular filtration rate and the renal blood flow. In the cases with no or only mild vascular changes, the renal clearances were normal or only slightly reduced. The filtration fraction was normal in these two groups, a fact which indicates the absence of constriction of the efferent glomerular arterioles in the early stages of hypertension (197). Other authors have reported studies showing also that the renal clearances may be normal in a high proportion of subjects with uncomplicated essential hypertension (198) and that the decrease in renal blood flow when it is present is shared equally by the two kidneys (199). It must be emphasized that to demonstrate the presence of renal ischemia the ratio of renal plasma flow (diodrast clearance) to tubular excretory mass (tubular maximal secretion of diodrast) should be calculated, the reduction of diodrast clearance not demonstrating necessarily that renal ischemia is present (199).

The mathematical treatment of data obtained from the literature has led Lamport to the conclusion that in essential hypertension afferent arteriolar constriction outweighs efferent constriction. It seems likely that the resistance of the afferent arterioles varies with blood pressure so as to preserve renal function and this change obscures the specific effect of the pathological condition on the glomerular arteries (8).

No significant change in renal clearances follows the various types of sympathectomy (200, 197) even in those cases in which the blood pressure falls (200). Some new reports have appeared on

the results obtained by the surgical treatment of hypertension (201, 202, 203).

Other renal functions may be changed in essential hypertension; tubular reabsorption of chloride (204) and the ability of the kidneys to concentrate urine and to excrete phenolsulphonephthalein have been found to be reduced (205).

ECLAMPSIA AND TOXEMIAS OF PREGNANCY

The role of the kidneys in the production of toxemia of pregnancy is still a matter of discussion. The histological examination of a kidney removed during pregnancy revealed widespread and marked medial hypertrophy especially in the afferent arterioles which is hypothetically attributed to some hormonal influence during pregnancy (206). A decreased kidney function as evidenced by a diminution in the clearance of inulin and diodrast can be demonstrated in eclampsia (207). Urea clearance and uric acid clearance are also decreased probably as a result of decreased glomerular filtration (208). These results suggest that the hyperuricemia of preeclampsia and eclampsia may be due to the decrease in uric acid clearance (208).

On the basis of data obtained in the literature Lamport concludes that a reduced filtration fraction exists in toxemia of pregnancy. As both the elevated blood pressure and the low blood protein (209) should lead to high filtration fraction the finding of a reduced C_{in}/C_D indicates a specific renal effect of the toxemia (8). But not all investigators agree in that the filtration fraction is decreased in toxemia of pregnancy or eclampsia (207). Perhaps a better definition of the term toxemia of pregnancy would clarify the situation.

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BLOOD

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Even with the drastic reduction of research, numerous articles on blood are still appearing, thus making it exceedingly difficult to present adequately a comprehensive review of the whole field of hematology. The reviewer has therefore limited himself to one phase of the subject, namely, coagulation, because this topic continues to attract major interest since its renaissance in 1934. In preparing this review, some of the original articles could not be consulted and only abstracts were available. The literature up to the latter part of 1941 is reviewed in the writer's monograph (1). Recent literature to 1942 is covered by the articles of Smith (2) and Brunner (3). Bethell, Sturgis and their associates (4) have again comprehensively reviewed the clinical contributions to hematology.

THE COAGULATION OF THE BLOOD

Theories.—The classical concept that thrombin is formed by the action of thromboplastin (derived principally from disintegrating platelets) on prothrombin in the presence of ionic calcium is again vigorously attacked. Ferguson (5) postulates clotting centers about the proteases of the blood which during normal circulation are inactive. In shed blood colloidal disturbances bring about the liberation of tryptase which in conjunction with ionized calcium and free phospholipid, cephalin, functions as the agent which activates prothrombin. Excess tryptase digests prothrombin and thrombin; therefore it also constitutes the antiprothrombin and antithrombin; and this enzyme likewise digests fibrinogen and fibrin, thus making the term, fibrinolysin, superfluous. The natural anticoagulants are tryptase inhibitors. Ferguson makes no attempt to fit into his unified concept recent work of other investigators on antithrombin, metathrombin, calcium, and the quantitative relation of thromboplastin to prothrombin activation.

The old observations that oxalated blood can be made to clot by shaking with chloroform and that the fibrin formed dissolves on standing has in the hands of Tagnon (6) led to new and inter-

esting findings. Recalcified plasma treated with chloroform for one hour develops a thrombin activity far in excess of normal serum, and it has some fibrinolytic power. If the serum is in contact with chloroform for twenty-four hours, the fibrinolytic power is enhanced causing the fibrin to be lysed so quickly that no clot is observed. From the chloroform serum an enzyme similar to or identical with trypsin can be obtained by acidifying the highly diluted serum. It activates prothrombin in oxalated plasma, i.e., without the intervention of calcium or thromboplastin. The fact that such an enzyme can be extracted from cellfree plasma is good evidence according to the author that it plays a primary role in coagulation. In an extension of this work Tagnon (7, 8) demonstrates that when platelet-free decalcified human plasma is treated with chloroform, a fraction of the plasma globulins yields an enzyme similar to trypsin in its action. It can lyse both fibrin and fibrinogen as well as casein and gelatin and can convert prothrombin to thrombin. Grob (9) finds that serum antitrypsin inhibits the coagulation of plasma *in vitro* and that its action is antiprothrombic. Iyengar (10) reports that an inverse proportion exists between the clotting time and the trypsin content of plasma. According to this investigator platelets but not red cells contain trypsin kinase which liberates trypsin from an inhibitory component.

Further evidence that prothrombin can be converted to thrombin without calcium, platelets, or thromboplastin is brought out by Adams & Taylor (11). Following Parfentjev's procedure, they obtained from citrated beef, swine, and human plasma by a salting out and subsequent dialysis a preparation consisting of the pseudoglobulin fraction which possesses strong thrombic activity. Unfortunately the name "clotting globulin" often used to designate this agent is apt to be confused with the globulin substance of Patek & Taylor which is thromboplastic in nature. These findings naturally lead to the question whether platelets or thromboplastin play any direct role in coagulation. Lozner & Taylor (12) present convincing evidence that the effect of various foreign surfaces on the clotting time is not due to lysis of platelets. They believe that a surface such as glass can cause a physicochemical modification of one or more plasma constituents, particularly the euglobulin fraction forming active plasma thromboplastin.

THROMBOPLASTIN

In view of the foregoing discussion, it is apparent that knowledge concerning the nature and action of this agent is becoming more confused. Widenbauer & Reichel (13) find that removal of lipides from brain extract destroys its coagulating activity, whereas extracts of other tissue show no change in activity when deprived of lipides. This the authors interpret as demonstrating that two classes of thromboplastin exist: protein and lipides, rather than a single protein-lipide complex. These authors (14) doubt that platelets are an important source of thromboplastin. Widenbauer (15) believes that thrombokinase is inactivated by a high tension of carbon dioxide and therefore plays an important function in hemostasis. Chargaff and his co-workers (16) are continuing their studies of thromboplastin from ox lung. By means of ultracentrifugation they have obtained a lipoprotein with a high molecular weight having strong thromboplastic activity. Dyckerhoff *et al.* (17) report finding a prothrombin-activating factor in aged yeast extracts.

Astrup & Darling (18) propose standardizing thrombokinase activity by its effect on the clotting of recalcified plasma. They find heating extracts of ox lung to 40°C. increases its activity while filtration and centrifugation reduce its potency. Copley (19) reports that the thromboplastic activity of dehydrated rabbit brain does not reach its maximum until the animal is six weeks old. Rather than accept the concept that the clotting time of recalcified plasma in the presence of excess thromboplastin is a direct function of the prothrombin concentration, he reverts back to the Howell theory that prothrombin is kept inactive by heparin and a complementary factor and that thromboplastin neutralizes heparin. Reasons for rejecting this theory have been outlined by the reviewer (1). Thromboplastin can be preserved by keeping it in the frozen state (20, 21). Human milk as a source of thromboplastin is used for determining prothrombin (22). Pyrrole is employed to inhibit the peroxidases which would otherwise destroy the thromboplastin. Katzenstein & Arnold (23) observe that injection of thromboplastin into dogs produces cerebral lesions similar to those caused by histamine but rarely lead to vascular occlusion. Shafiroff *et al.* (24) believe that the hypercoagulability following severe hemorrhage is due to a mobilization of thromboplastin.

FIBRINOGEN

Laki (25) reports the isolation and crystallization of fibrinogen from pig plasma. The crystals are needle-shaped and form aggregates. To the writer's knowledge this is the first report of isolating crystalline fibrinogen. Bailey *et al.* (26) show by means of x-ray diffraction patterns that fibrinogen is structurally similar to the fibrous proteins of the epidermis, the keratinous tissue, and the chief muscle protein, myosin. All spring from the same peculiar shaped molecule. Fibrinogen has a much greater influence on the fluidity of blood per unit of concentration than the other blood proteins which again is probably a manifestation of its peculiar structure (27). Bucher (28) detects differences in the fibrins from different species by microscopic examination of fixed and stained sections. Mylon and his associates (29) have developed a new method for the determination of fibrinogen by precipitating it with protamin.

Fibrinogen can influence coagulation due to possessing a certain degree of species specificity (30). With increasing concentrations of sodium chloride, coagulation of fibrinogen by thrombin is prolonged, but a more important effect is on the conversion of prothrombin to thrombin (31). Witts (32) finds that the prothrombin time, which he calls "accelerating clotting reaction," is not significantly influenced until the fibrinogen falls below 30 per cent of normal. Page and his associates (33) find little correlation between the prothrombin time and the usual variations of fibrinogen concentration. Fibrinogen can be made incoagulable by the action of certain drugs and chemicals. According to Crut (34) the anticoagulant action of sodium anetholesulphonate can be thus explained. Chargaff & Bendich (35) report that in addition to ninhydrin, they find other compounds (chloramine T, 1-4-naphthoquinone-2-sulfonate and 1,2-naphthoquinone-4-sulfonate) capable of coagulating fibrinogen. The authors do not claim that the clotting of fibrinogen by thrombin and these agents is identical, but they make the pertinent comment that both reactions are oxidative. Ferguson & Ralph (36) have studied the coagulation of fibrinogen with the dark-field microscope and find that the fibrin clot produced by thrombin and papain are similar in appearance while those caused by ninhydrin are quite different, and therefore they consider the latter of no significance in the coagulation mechanism.

Sometimes a purely utilitarian objective yields data of pure

scientific interest. Dees (37), in developing the idea of using an intrapelvic coagulum for the purpose of enmeshing and thereby removing renal calculi, chose fibrinogen as the most suitable medium. With the aid of Neurath & Fox (38, 39) he determined optimum conditions for obtaining fibrinogen which yields clots with maximum tensile strength. Pure fibrinogen yields a mechanically stronger clot than plasma or whole blood. Tarlov and his co-workers (40, 41) studying the problem of autologous plasma clot sutures of nerves, likewise investigated the tensile strength of clots. Plasma instead of fibrinogen solution was used. Clot retraction does not appear to influence the tensile strength, but the initial concentration of fibrinogen does. Lalich & Copley (42) also describe a method for testing clot firmness by the pressure required to force a clot through a viscometer tube.

Fibrinolysin.—There is no evidence that normal blood contains any appreciable amount of fibrinolysin, yet mere treatment of plasma with chloroform will readily cause its appearance (6). Proteolytic enzymes appear to be responsible for the fluidity of menstrual blood. Lozner *et al.* (43) conclude that it is blood which has clotted and had its fibrin removed during the slow passage from the uterus. Huggins and his co-workers (44) find that fresh menstrual blood has definite fibrinolytic activity and contains small amounts of trypsin. Curiously, rat uterine fluid is strongly fibrinolytic and also digests fibrinogen. Huggins & Neal (45) find that both human and canine semen contain a fibrinolysin which will dissolve the fibrin of normal subjects but not of patients with various diseases. The semen of the dog has a pronounced capacity for digesting fibrinogen, i.e., a high fibrinogenase activity, whereas human semen has little, but does possess a much higher fibrinolytic potency. The authors feel that fibrinolysin and fibrinogenase are distinct and separate entities. Huggins & Vail (46) find that dog prostatic secretion clots oxalated rabbit and beef plasma. Heparin does not prevent the action. Human plasma is not clotted since the fibrinogen is too rapidly destroyed by fibrinogenase. Oxalated plasma is not coagulated by human prostatic fluid.

Ferguson (47, 48) employed both the fibrinolytic and the fibrinogenolytic action of trypsin for the quantitative determination of the enzyme in blood.

The fibrinolysin of the hemolytic streptococcus presents several points of interest. Yannet & Leibovitz (49) found that, follow-

ing an outbreak of hemolytic streptococcal infection, approximately 85 per cent of the patients developed an antifibrinolysin factor in their blood which gradually disappeared in the course of six months. The duration and severity of the infection did not appear to have had any influence on the production of this factor and subjects who did not develop it did not differ clinically from those who had a strong positive response. The significance of this immunological response is difficult to determine. It will be interesting to watch further developments of Neter's (50) observation that tyrothricin and acinomycin inhibit fibrinolysin of the beta hemolytic streptococcus and the coagulation of plasma by pathologic strains of staphylococci. The first agent contains gramicidin while the latter is similar to penicillin.

Perhaps much of the work on fibrinolysin must be reconsidered on the basis of Milstone's (51) finding that highly purified fibrinogen is not lysed by streptococcal fibrinolysin unless a small amount of human serum is added, a fact indicating that a lytic factor in the euglobulin is essential for the activity of fibrinolysin. Boisvert (52) shows that in newborn babies the resistance of the fibrin clot to fibrinolysin is not due to an antilytic factor such as occurs in patients recovering from a hemolytic streptococcal infection, but to the absence of the lytic factor of Milstone. The clot from the blood of newborns readily dissolves when tested with streptococci provided human serum is added. Lichty & Anderson (53) record similar findings. Of fifty infants studied thirty-six showed clots which had no resistance to lysis; six had positive antifibrinolysin and eight lacked the lytic factor.

PROTHROMBIN

Evidence is presented by Quick (54), that prothrombin is a complex consisting of two components which are combined through calcium. One of these factors, component A, diminishes from oxalated or citrated plasma on storage, presumably by oxidative destruction. Component B disappears from the blood in dicumarol poisoning and perhaps also in avitaminosis K. The factor can be removed from plasma with aluminum hydroxide. In unaltered blood or plasma, no diminution of component A occurs, nor can component B be adsorbed and removed by aluminum hydroxide. This indicates that the two components are combined and stable. Removal of calcium liberates them. Rabbit blood is

found to require more sodium citrate than human blood to become incoagulable in the presence of excess thromboplastin, which is in accord with the finding that the prothrombin concentration of rabbit blood is much higher than that of human. Prothrombin is considered a protein calcium complex which is slightly ionized.

The new concept of prothrombin may furnish a possible clue to the difference in the one- and two-stage methods for determining this agent. Since decalcification disrupts the prothrombin complex, recalcification must cause a resynthesis. Dilution of the plasma can conceivably affect this resynthesis. In the original one-stage method the plasma is not diluted, but in Link's modification using undiluted and diluted (12.5 per cent) plasma distinct variations in the differences between the prothrombin times of the two plasmas are observed in some clinical conditions (55, 56, 57). The two-stage method is found by Warner and his associates (58, 59, 60) to yield low results in pernicious anemia and in various types of liver disease, whereas the one-stage procedure gives fairly normal results. Does a real hypoprothrombinemia exist in these conditions, or does the high dilution of the plasma cause physicochemical changes that reduce the yield of thrombin? Witts (61) comments that the physicochemical objections to the two-stage method are not adequately considered.

Modifications of the one-stage method continue to appear. Stein (62) rightly emphasizes the need for uniformity in expressing prothrombin activity. Russell viper venom is used by Iyengar & Sehra (63), but most investigators continue to employ rabbit brain.

The disappearance of prothrombin from stored plasma continues to be studied. Page & deBeer (64) note that the rate of diminution is directly affected by the temperature. Villela (65) states that decalcified plasma loses 40 to 50 per cent of its prothrombin in forty-eight hours. The loss can be minimized by storing plasma at 0°C. (66) or by lyophilizing plasma (67). The fact that only component A is lost in storage and that component B is almost always the one which is diminished in the body (54) suggests that stored plasma may be found to be as effective as fresh blood or plasma to combat hypoprothrombinemia.

Prothrombin and vitamin K.—An excellent and authoritative review covering the development of vitamin K from its beginning in 1929 to 1941 has been written by the man most eminently

qualified, namely, Dam (68). Prothrombin deficiency as the cause of hemorrhage in avitaminosis K is now unequivocally accepted by most investigators, but there are dissenters. Maltaner & Maltaner (69) on the basis of experiments involving the use of cephalin tissue extracts, and sera of various animals in studying the blood of vitamin K deficient chicks conclude that diminished prothrombin does not adequately explain the delayed clotting. Many of the papers now appearing are the result of work begun before the full fury of the war struck. Orla Jensen *et al.* (70) demonstrate that *E. coli* is the most potent producer of vitamin K of all the common intestinal bacteria. In young chicks *E. coli* grows slowly and is apparently aided in its growth by the presence of vitamin K in the intestines (71).

Since the introduction of synthetic compounds having strong vitamin K activity, little attention has been given to the natural vitamins. Davis and his collaborators (72) find that the oxide of vitamin K₁ has a rapid and prolonged action. Scudi (73) reports that vitamin K₁ is stable when mixed with blood and does not produce methemoglobin, whereas menadione (2-methyl,1,4-naphthoquinone) is rapidly destroyed by blood *in vitro* and causes methemoglobinemia. Honey possesses definite vitamin K activity (74) as does the European mountain ash berry (75). Barnes (76) finds that Congo red improves the hypoprothrombinemia induced by the addition of mineral oil to the diet. Grodins & Ivy (77), correcting an earlier report, state that vitamin D has no beneficial effect.

The action of vitamin K in the production of prothrombin is still unsolved. The old observation that excess vitamin K does not elevate the level above normal is again confirmed (78). Adams (79) finds a marked increase of prothrombin in women during the latter part of pregnancy. A similar finding is observed in pregnant rats (80). Pakendorf *et al.* (81) believe that only the oxidation products of vitamin K are the effective factors and comment that the active quinones yield phthalic acid on oxidation. Warren (82) makes the pertinent suggestion that menadione may react with the sulfhydryl groups, which some believe play an important part in coagulation.

The amount of vitamin K needed by the growing animal is surprisingly small. Stamler *et al.* (83) find that a chick requires only 1 to 2 μ g. of menadione a day. There is no increased demand for vitamin K as the animal increases in weight. Since the amount

needed is small, the danger of toxic reactions is very remote. Ansbacher and his co-workers (84) find that large amounts of synthetic vitamin K must be given before harmful effects are noted. Injury to the circulating red cells is the outstanding finding. Vitamin K is needed by cold blooded animals. In the turtle the prothrombin time increases during hibernation but can be reduced promptly by the administration of small amounts of vitamin K (85). The production of hypoprothrombinemia in mammals by diet has always been found extremely difficult. Moore *et al.* (86) report successfully producing such a deficiency in rabbits and thereby inducing abortion. On giving vitamin K pregnancy proceeded normally. Javert & Stander (87) believe that in certain cases of threatened abortion in humans, deficiency of vitamin K and C may be factors. Baldwin and his co-workers (88) find that vitamin K has a protective action for the chick against the hemorrhage caused by infection with *Eimeria tenella* but record no prothrombin studies.

Vitamin K in the newborn.—A monograph on hemorrhage in infants by Franconi (89), a student of the subject long before vitamin K was known, is a timely contribution. Kato (90) also has written a review. It is now generally recognized that the prothrombin falls in newborn babies and that this physiological decrease can be prevented by vitamin K given to the mother shortly before the baby is born. Studies substantiating this continue to appear (91 to 98). Sanford and his associates (99) and Parks & Sweet (100) report that vitamin K has not reduced the incidence of neonatal bleeding. The paper of Sanford with its provocative title: "Is the Administration of Vitamin K to the Newborns of Clinical Value?" has prompted a number of investigators to reiterate the positive value of vitamin K (101 to 105). That factors other than low prothrombin are also responsible for bleeding in the neonatal period is emphasized by Scobbie (106) and by Poncher (107). Moloney (108) finds that a high percentage of newborns shows an abnormal capillary fragility, which gradually disappears. Webster & Fitzgerald (109) continue to present evidence that barbiturates contribute to a hypoprothrombinemia in both mother and baby, and emphasize the prophylactic value of vitamin K. In another paper (110) they report that out of 5,370 obstetrical cases, forty-four babies developed signs of hemorrhage. Of these only two were born of mothers who received vitamin K. Smith & Warner (111) critically analyze some of the factors, such as influence of season and social status,

that may be responsible for variations in the prothrombin level of newborns. Hypoprothrombinemia and a bleeding condition can occur in babies with congenital pyloric stenosis (112).

Prothrombin level and liver damage.—The role of the liver in the production of prothrombin is further illustrated by studies of Uvnäs (113) who noted a marked drop when the organ was excluded from the circulation. An interesting case of a newborn baby is reported (114) in whom an intractable hypoprothrombinemia was found to be due to an extensive infarct of the liver. Andrus & Lord (115) describe a simple method for producing hepatic injury and hypoprothrombinemia by injecting chloroform into dogs, and they present a comprehensive review of the relationship between liver function and the prothrombin level.

The prothrombin response to vitamin K as a test of liver function, and especially as a means to differentiate obstructive or "surgical" from toxic or "medical" jaundice, has received further study (116 to 119). Opinions vary as to the sensitivity of the test. Sweet and his co-workers (120) note that the test corresponds well with the degree of parenchymal injury while White and his group (121) consider the determination of secondary importance as a test of hepatic function since it does not correspond accurately to the degree of liver dysfunction established by other means. It has already been mentioned that the two-stage method yields low results in certain liver conditions while normal findings are recorded with the one-stage method (60). Kapnick *et al.* (122) recommend that the prothrombin test be used to detect early liver damage in patients receiving sulfonamide therapy. Depression of liver function secondary to diseases of other organs may occur. Longo (123) finds no marked prothrombin decrease in hyperthyroidism. Sproul & Sanders (124) report that when cats are deprived of the external secretion of the pancreas a moderate and irregular reduction of prothrombin occurs and the vitamin K of the livers of these animals is reduced.

The hypoprothrombinemia in tuberculosis is still poorly understood. Sheeley (125) believes that toxemia is responsible while Levy (126) reports that parenchymal liver damage is frequently found. A progressive improvement in prothrombin occurs following successful collapse therapy (127).

It is now recognized that a hypoprothrombinemia can occur without any apparent cause. Van Crevald (128) reports a case

that did not respond to vitamin K, while Shinowara *et al.* (75) studied a patient that did benefit when given synthetic vitamin K. Giordano (129) reports a case which appears familial since other members of the family have low prothrombin levels. The writer (54) has found a consistent prothrombin level of 45 per cent in a medical student who is normal in all other respects.

Thrombin.—Efforts to obtain a pure preparation of thrombin continue. Seegers & McGinty (130) find their highly active product can be separated into two fractions differing in solubility. Milstone (131) by a method differing somewhat from Seegers' has also obtained a highly potent preparation, which is soluble in 0.45 saturated ammonium sulfate. Seegers & Smith (132) discuss the various factors, especially species specificity that must be considered in the assay of thrombin. Astrup (133) likewise considers the factors that influence thrombin action. It would be interesting to have a comparative study of true thrombin and the clotting globulin of Parfentjev, which has now been prepared from various bloods (11). Kauer and co-workers (134) confirm older observations that *Bothrops atrox* venom clots both oxalated blood and fibrinogen and that when injected causes a marked depression of the circulating fibrinogen and prothrombin. The use of thrombin as a hemostatic agent is continuing to receive attention (135, 136) and it is reported that the Russians are preparing it in volumes of thousands of quarts (137).

ANTICOAGULANTS

Antithrombin.—Grünning (138) reports that the active agent can be extracted from the albumin fraction with ether, and concludes that it is a lipoid, not a protein. Nevertheless its activity is destroyed at 50°C. Astrup & Darling (139) describe a method for estimating the antithrombin which consists in the incubation of a fixed amount of thrombin with varying quantities of serum and then determining the thrombin remaining. With this method Volkert (140) studies the variation of antithrombin in various experimental conditions. He concludes that there are two antithrombins: a constant plasma factor related to albumin, and heparin plus a co-factor. Seegers & Smith (141) describe another method in which a definite amount of heparin is added to the plasma before thrombin is added. They state on the basis of earlier work (142) that heparin merely accelerated the reaction. This must be inter-

preted to mean that antithrombin and the co-factor of heparin are identical which is contrary to the concept of the Danish investigators. Wilson (143) has also made a quantitative study of the antithrombin of the blood.

Assay of heparin.—Seegers (144) utilizes the finding that a direct proportion exists between the amount of thrombin required to clot plasma in fifteen seconds and the quantity of heparin added. Kuizenga & Nelson (145) merely add heparin to sheep plasma and recalcify. Copley & Whitney (146) describe a method based on the amount of toluidine or azure A that is decolorized. The difficulty of assaying heparin is increased by the fact that heparins from various species differ (147) and that the highly purified product can be separated into separate fractions (148).

Heparin does not prevent the clotting of citrated blood by the coagulase of various strains of staphylococci (149). Rigdon & Schrantz (150) find that phagocytosis of carbon particles by the cells of the reticuloendothelial system of rabbits is not inhibited by relatively large doses of heparin. Dragstedt *et al.* (151) show that heparin in doses much larger than are needed to inhibit clotting prevents the release of histamine from cells in anaphylactic shock and allied conditions. Since these workers (152) have found that the injection of trypsin causes release of heparin, it may mean that this outpouring is a protective mechanism. Landis and his co-workers (153) report that the vasoconstrictive action of defibrinated blood is partially depressed by heparin and that the pressor substance is entirely absent in heparinized plasma. Hahn (154) records that alimentary lipemia can be abolished often in one minute after injecting heparin. Macht (155) finds that it lowers the toxicity of digitalis and ouabain in experimental animals, and furnishes protection against anaphylactic shock.

No attempt will be made to review the clinical uses of heparin, but a few interesting observations should be cited. Wound healing is not influenced by this agent (156) and the rate of blood flow (as the result of changes in viscosity) is not increased (157). De Takats (158) observes that the effectiveness of heparin varies in different individuals. Loewe *et al.* (159) describe a method of administering heparin (incorporation in a slowly absorbed medium) which prolongs the action of the agent. When injected intravenously heparin is excreted rapidly—as much as 10 to 35 per cent in two hours (160).

Miscellaneous anticoagulants.—The salts of rare earths are effective agents for making the blood incoagulable, but their toxic action precludes clinical use (161). Vincke & Schmidt (162) state that their action is antiprothrombic. Ferguson (163) describes a crystalline trypsininhibitor which acts as a weak antiprothrombin, antithrombin, and antifibrinolysin. It, like heparin, requires a co-factor present in serum albumin. An extract from *Gloiopeltis furcata* having heparin-like action (164) suggests the probability that a successful anticoagulant may perhaps be found in plants.

Dicumarol (3,3-methylene-bis-4-hydroxycoumarin).—This agent has been studied extensively during the past two years. It is not a true anticoagulant since it has no direct action on the coagulation mechanism. How it reduces the prothrombin of the blood is still unknown. The writer (54) has already stated that he found dicumarol only reduces component B of the prothrombin complex. In the study of the hypoprothrombinemia from dicumarol, various modifications of the one-stage method have been used, but in no extensive investigation has the two-stage method been employed. English workers, notably Macfarlane (165) and Witts (166), claim that the one-stage method is unsatisfactory in dicumarol studies. American investigators have not voiced any serious criticisms. Link (167) states: "The best argument for the Quick test is that through it the hemorrhagic agent in spoilt sweet clover hay was laid on the table in pure crystalline form." Nevertheless the desirability of a standardized and uniform procedure cannot be denied.

The prothrombin level in rabbits is found by Lehmann (168) to drop below 20 per cent in one or two days following 3 or 4 mg. of dicumarol per kilo of body weight. These data agree with the writer's unpublished results in which a reduction to 20 per cent in twenty-four hours, to 5 per cent in forty-eight hours or to 2 per cent in seventy-two hours is found in rabbits and dogs irrespective of the dose, provided it is above the minimal effective amount. Bollman & Preston's (169) findings differ somewhat since they state that the change in prothrombin, within limits, is proportional to the amount of dicumarol administered. The minimum effective oral dose in humans is according to Meyer and his co-workers (170) 5 mg. per kilo of body weight with subsequent daily doses of 1.5 mg. per kilo. All agree that vitamin K in the usual therapeutic doses has little beneficial effect on the hypoprothrombinemia induced by dicumarol. Davidson & McDonald (171) failed even after

giving 60 mg. of synthetic vitamin K parenterally, but later report (172) that vitamin K₁ oxide in doses as high as 250 mg. did prevent or reverse the hypoprothrombinemia produced by a single dose of dicumarol. It appears that when a minimal amount of the agent is administered, vitamin K can counteract to some extent the deficiency of prothrombin both in animals (173) and in man (174). Perhaps the finding of Overman (173) that ascorbic acid alone, or better when fed with synthetic vitamin K, drastically counteracts the hypoprothrombinemia of dicumarol may furnish an answer to this problem.

Dicumarol does not cause liver damage when given in therapeutic amounts (169, 171, 174 to 178). The presence of liver damage, however, causes dicumarol to become more potent and prolonged in its action (169, 179, 180). Kidney dysfunction also exerts a similar effect (169, 180). When dicumarol is given to rats following anesthetic doses of chloroform, pentobarbital, and pentothal, the fall in prothrombin is no greater than is observed in unanesthetized animals (181). Fever causes rats to become more susceptible to the drug (182). Curiously, lactating rats are unusually resistant to the action of dicumarol (183). In humans the bleeding time is not prolonged even after marked prolongation of the prothrombin time (171) and Butsch & Stewart (184) even performed herniorrhaphies on a series of patients with prolonged clotting times and decreased prothrombin without encountering serious bleeding. The prolonged bleeding time observed in mice (185) may perhaps be explained on the basis of the method used. Wright & Prandoni (177) stress that no increase in capillary fragility occurs, while Bollman & Preston (169) record a widespread dilatation of the small blood vessels of the liver. Cahan (186) reports a case of purpura caused by dicumarol with prolongation of both bleeding and clotting times. Such a reaction must be considered as exceptional. It is claimed (176) and denied (177) that the sedimentation rate is increased by the action of the drug.

The temporary effectiveness of fresh blood transfusions in treating the hypoprothrombinemia due to the dicumarol is well established. Cahan (186) found citrated banked plasma beneficial in one patient, while Wright & Prandoni (177) did not find stored plasma effective. According to the concept that prothrombin is a two-component complex (54), stored blood should be as good as fresh. McGiaty *et al.* (187) report the effective action of purified

beef prothrombin on elevating the depressed prothrombin level in dogs fed dicumarol.

Salicylates and hypoprothrombinemia.—Link and his associates (188) note that rats given salicylates develop a hypoprothrombinemia which they can prevent with synthetic vitamin K. Rapport *et al.* (189) likewise find this to be true in rabbits, dogs, and humans. Meyer & Howard (190) record that in man relatively small doses produce a moderate degree of prothrombin depression which vitamin K entirely prevents. They use the one-stage method without diluting the plasma. Shapiro and his co-workers (191) employing the diluted plasma (12.5 per cent) modification obtain essentially the same results. They stress the possibility that liver damage may intensify the action of salicylates. They suggest combining salicylates and dicumarol for clinical use. In none of these studies is the actual mechanism of salicylates determined, but the inference is made that the action is similar to that of dicumarol. Two other compounds which can induce a hypoprothrombinemia are sulfaguanidine (192) and dihydroxystearic acid (193).

PLATELETS

Copley & Robb (194) have modified the Vilaríño and Pimental method for counting platelets, and with this procedure find that heparin reduces the number of platelets both *in vitro* and *in vivo*. Baronofsky & Quick (195) find no agglutination or reduction of platelets in blood containing large amounts of heparin. The platelet count may vary in different parts of the vascular system and it is reported (196) that the count may be markedly decreased in a diseased extremity, particularly in the legs and feet. This finding can perhaps be correlated with the observation that the coagulability of the blood in the lower extremity, especially in vascular diseases, is increased (197).

The significance of platelet agglutination is receiving more attention. Wright (198) finds that stickiness of platelets increases after surgical operations, and believes that this is due to the liberation of young cells. Altschule (199) describes a case of thrombocytopenic purpura in which a widespread formation of platelet thrombi occurred. The agent which produces the agglutinating effect has not been identified. The isolation of a specific substance from the spleens of patients having essential thrombocytopenic purpura has not been accomplished, but encouraging

progress is recorded (200 to 202). Uihlein (202) makes the interesting comment that the reaction "suggests the presence of anaphylaxis or a histamine reaction." It is unwise to ignore the factor of allergy in platelet agglutination. Turnbull (203) demonstrates a definite relationship between certain cases of spontaneous thrombosis and allergy. Unfortunately he records no platelet counts. Thrombopenia from various drugs particularly the sulfonamides are reported with increasing frequency (204, 205, 206). A peculiar acute thrombocytopenic purpura is found in the West African disease, onyalai (207). Morlock & Hall (208) call attention to the fact that a decrease in the platelet count may occur in hepatic diseases, particularly in cirrhosis, which may increase the bleeding hazard.

Capillary fragility.—Not only is the subject of capillary resistance complicated but methods of study are not altogether trustworthy. Bell *et al.* (209) on comparing the positive (Göthlin) with the negative (Dalldorf-Russell) pressure resistance tests found poor correlation, and little help for interpreting the effects of vitamin C and P on the fragility of the capillaries. Lucia & Aggeler (210) present a pseudohemorrhagic diathesis that they call "simple easy bruisability" in which all the common tests are normal. They believe thyroid dysfunction may be related to this type of capillary weakness.

Vitamin P has been further investigated. Bacharach and co-workers (211) have developed a biological test for this vitamin. Guinea pigs on a scorbutogenic diet show decreased capillary resistance which can be prevented by a water soluble preparation of vitamin P, but not by vitamin C alone. There seems to be no correlation between the distribution of vitamins P and C in plants (212). Cameron & Mills (213) record a case of adult scurvy in which the hemorrhagic features disappeared when vitamin P alone was given. The vitamin is a part of an oxidation reduction enzyme (214). Scarborough (215) states that the agent is specific only if a definite deficiency exists and is not effective against various types of purpura such as arsenical. A review of the function of vitamin P is presented by Lindheimer *et al.* (216). Franke (217, 218) shows that capillary fragility may occur in jaundice which responds to vitamin K. Aggeler and his associates (219) report a case of purpura from anorexia nervosa caused by vitamin K deficiency.

A better evaluation of the bleeding time should result from

Scarborough's (220) observation that in hemophilia a normal value is obtained until the cut is about 6 mm. deep. This may perhaps explain the prolonged bleeding time in the hemophilia-like disease of swine (221) and mice (185) since the method of Copley & Lalich (222) depends on a deep puncture wound. Clot resistance tests are described by Lalich & Copley (223) and by Aggeler *et al.* (224, 225) who also discuss clot retraction and its significance in hemostasis. Hirschboeck & Coffey (226) present evidence that rapid clot retraction is a prognostic sign of thrombosis.

HEMOPHILIA

The disease has a special interest to the physiologists since its solution would furnish an important clue for unravelling the mystery of coagulation. In 1943 three distinctly different explanations for hemophilia have been offered. Tagnon *et al.* (227) conclude that the proteolytic activity of hemophilic blood is less than normal. Ferguson (5) voices a similar view, namely that a plasma defect in available protease exists. Pennell (228) presents a radically new idea that the fault may be in the hemophilic erythrocytes, since the conjugation between platelets and red cells which he finds occurs in normal shed blood is markedly diminished in hemophilic blood. The essential idea is that the red cell serves as a surface that functions in the disintegration of the platelets. Tocantins (229) shows by means of simple experiments that thromboplastin when incubated with plasma is destroyed or inactivated, and that this antithromboplastic activity is very marked in the plasma of the hemophiliac. He proposes that the delayed clotting is due to a destruction of thromboplastin, which is faster than its liberation from platelets. It will be noted that the latter two hypotheses center about the platelets, while the first entirely excludes the formed elements of the blood.

The results of therapy throw no light on the clotting defect in hemophilia. Copley & Lalich find *Bursa pastoris* effective. This plant contains much oxalic acid, which Blain & Campbell (231) claim is an effective hemostatic agent. Tagnon & Taylor (232) claim that the clotting time in hemophilia is reduced when rabbit thrombin is given orally. Injection of lyophile human plasma reduces the clotting time, but lyophile hemophilic plasma does not (233). The successful use of ascorbic acid in a hemophilic patient illustrates that sometimes capillary weakness may complicate the

disease (234). Birch (235) finds that there is not sufficient variation in the excretion of estrogenic hormone between hemophiliacs and normal males to be of significance.

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Nervous control.—A subject of careful study was the respective roles of the sympathetic and vagal innervation in heart rate changes in dogs and cats startled by noise (1). Heart action was electrically recorded, together with respiratory movements, in intact animals and also twenty-four or more hours after exclusion of the adrenals and section of the vagi or the sympathetics. Following sound stimulation in the normal animals the rate rose within the time of one cycle or less from 60 to 100, to over 200 per min. In some animals the first few beats, often from an ectopic focus, reached 300 per min. In dogs, the rate often fell after about ten seconds to below the control rate, unless this was slow, and then rose slightly, and remained high, with fluctuations, for over half a minute. This more enduring tachycardia was due to epinephrine. Denervation of the carotid sinus abolished both sinus arrhythmia and the rapid rate fall after the period of greatest acceleration. This operation did not modify the response in sympathectomized animals. Following sympathectomy the resting heart rate was 48 to 60 beats per min. With noise, the rate began to rise, often within the first beat, to 100 or 110 per min., the cycles being only slightly shorter than the shortest cycles in the same dogs before stimulation. Sinus arrhythmia disappeared. In a few dogs, the first response was 4 or 5 beats at 200 to 350 per min., often ectopic in origin. After vagotomy, the resting heart rate was 120 to 130 beats per min. Upon stimulation it rose as in normal animals but fell more slowly returning (in dogs) to control levels within twenty-five to thirty seconds. In another paper the resting heart rates of dogs under nearly basal conditions was reported to range from 50 to 56 per min. Sympathectomy left these rates essentially unchanged (2). In a few, but not in all, atropinized, chronically sympathectomized cats, stimulation of the peripheral end of the vagus nerve, cut in the neck, may cause acceleration of the heart. Paralysis of the middle cervical ganglion by nicotine abolishes the effect, which is attributed to the formation of synaptic connections between

preganglionic vagus fibers and denervated cells of the middle cervical after avulsion of the stellate ganglion (3).

In a study of the relation between heart rate and respiration in six human subjects, four procedures were used: (a) full, deep, inspiration with and (b) without decreased intrapulmonary pressure; (c) full expiration with, and (d) without decreased intrapulmonary pressure. Only procedure *b* caused a significant slowing of the heart during thirty seconds. This is attributed to the inspiratory position of the chest. In procedure *a*, accelerator influence offset the slowing (4). A human syndrome is described in which there is failure to get the usual heart slowing upon immersion in cool water (5). The reclining, but not the standing, pulse rate is reduced by twenty-four hours of sleep loss (6).

Inhalation of ammonia slows the rabbit heart to fifty-five beats per min. Advantage was taken of this response to make cardiac slowing a conditioned reflex effect, the conditioning stimulus being the sound of a bell. The fall in rate, after a brief initial increase, was eighteen to twenty-four beats below the resting level of about 225 (7).

Cardiodynamics and heart sounds.—In a study of the differential effects of respiration on the two ventricles, the authors used a modification of the method of Boyd & Patras, which permitted the ventricles to operate against fluctuating negative intrathoracic pressures, but which also eliminated the possibility of respiratory displacement of the recording membrane. Confirming previous observations of a fall in mean arterial blood pressure in inspiration and a rise in expiration, the authors, from cinematographic pictures taken through a thoracic window, found that the explanation was a moderate increase in left ventricular output in expiration. This was associated with a marked expiratory decrease in the right ventricular stroke volume. On inspiration the effects were reversed. It is pointed out that the findings not only explain the respiratory fluctuations in arterial blood pressure, but that they are also compatible with the operation of Starling's law, each ventricle responding independently (8). It was also estimated that, under conditions of rapid intravenous infusion of saline, changes in respiratory phase, or compression of the aorta, a given increment in diastolic volume produced a larger increase in the stroke volume of the right than of the left ventricle (9). Under simpler conditions the foregoing interpretations were tested by use of a terrapin heart in an artificial

thorax (10). In a paper, of interest in this connection, an investigation of the one ventricle pump and the pulmonary arterial pressure of the turtle is reported (11).

Among 1,400 ballistocardiographic estimations of cardiac output, 100 patients were found to have a hyperkinemia, or output above normal. Hyperkinemia was almost always found in thyrotoxicosis, usually in patent ductus arteriosus, and often in emaciation. In seventeen patients no complicating condition was discovered (12). Some persons exhibiting the syndrome of neurocirculatory asthenia have hypokinemia (13); reduction in output usually follows myocardial infarction, reaching a minimum in two to four weeks with more or less recovery later (14). In angina pectoris the output is usually low.

Upon standing, as determined roentgenkymographically, only insignificant changes occur in cardiac stroke volume and output in individuals who do not faint within about twenty minutes. In persons who faint, on the other hand, the final reduction in stroke volume is 21 to 43 per cent, and in output, 25 to 35 per cent. This is attributed to lessened skeletal muscle activity (15).

That the emptying of the ventricles during systole is incomplete, i.e., that the residual ventricular volume is large, is obvious when the heart is dilated and the cardiac output is normal or reduced, as in congestive heart failure or myxedema. Under normal conditions, Starling's law implies an increase in residual blood under conditions of increased venous return or increased peripheral resistance, but it has not been shown to what extent inotropic sympathetic effects may modify the changes expected from the operation of that law. Roentgenographic evidence is now accumulating which indicates that even under resting conditions the residual volume, although not accurately measurable, is relatively large and that the residuum is increased in physical exercise, in paroxysmal tachycardia, and even upon change from the standing to the recumbent position (16, 17). The effect of residual blood upon circulation time measurements is pointed out (17).

From roentgenkymographic studies on man it is concluded that with reduction in oxygen in the air, corresponding to altitudes of eighteen to twenty-eight thousand feet, the minute output of the heart increases only slightly more than the increase in heart rate. Carbon dioxide (14 to 30 mm. Hg) tended to lessen the rate increase due to the oxygen deficiency, and the stroke volume again

remains practically constant. In neither case did the heart dilate. It is concluded that the heart is not the limiting factor in tolerance to acute oxygen deficiency (18).

By means of simultaneous recording of the phonocardiogram and the venous pulse, central arterial pulse, or EKG in fifty patients, it was shown that reduplication of the first heart sound was systolic in time in 82 per cent, and presystolic in the others. In the latter group, the P-R interval was long (19). The heart sounds produced by atrial activity in the long diastolic pauses of complete A-V block have two components. The first, attributed to ventricular distension, was more marked at the beginning of ventricular diastole; the second, more constant, sound is attributed to closure of the A-V valves at the end of atrial systole (20).

In a series of 126 persons with heart disease, but without decompensation, the mean score in the Schneider cardiovascular fitness test had almost the same range and mean value as among 138 normal controls (21).

Coronary flow.—By the thermostromuhr method it was shown that the increase in coronary flow during exercise in dogs with chronically sympathectomized hearts differs little from that in the intact animal; and the effects of exercise after full denervation were little different from those after vagotomy alone. In the absence of the vagi, only moderate acceleration occurred in exercise, whether the sympathetics were intact or not, and in these animals the chief factor regulating coronary flow appeared to be the arterial pressure (22). Atropine increases coronary flow after sympathectomy, but not after vagotomy or complete cardiac denervation. The increase is related to the augmented heart rate (23). By the use of the Gregg and Green flow meter it was shown in dogs that pitressin is a powerful coronary artery constrictor, reducing flow enough to depress the force of systole; and that epinephrine has an augmenting effect on flow only slightly greater than that due to the rise in intra-aortic pressure, an effect attributable in large part to the increased myocardial metabolism, to a slight dilator effect of the preservative of the epinephrine (chloretone and hydrochloric acid) and to a relative increase in total diastolic time (24). These two papers, using different methods, agree in finding the sympathetics unimportant as coronary arterial dilators; this stands in contrast to their chronotropic effect (1). Toxic, but not therapeutic, doses of digitalis lessen coronary flow (25).

Functionally significant intercoronary collateral circulation has been produced experimentally in pigs by coronary narrowing, without occlusion, as shown by absence of myocardial infarction following subsequent complete occlusion of the same artery, and by injection techniques (26).

Chemical changes and metabolism.—The chemical changes occurring in the rabbit heart during hypertrophy induced by experimental aortic insufficiency include a transitory rise in extracellular sodium and chloride, a fall to below normal levels after a few days, and a late (in about one-hundred days) return to control values (though chloride remains slightly low); a decrease in total potassium and acid soluble phosphorus; and a slight progressive rise in intracellular water for about thirty days. There is a tendency for the hypertrophied heart to lose intracellular constituents, especially potassium and phospholipin (27).

In well controlled experiments, pigs on thiamine-deficient diets showed a high blood content of pyruvic acid; the hearts were dilated, without hypertrophy; and death followed the signs of acute heart failure. Microscopic examination revealed focal and diffuse necrosis of the heart muscle, especially the atrial. The central and peripheral nervous systems were normal (28). In pigeons, thiamine deficiency produces signs of cardiac failure accompanied by tachycardia and myocardial necrosis. There is a marked decrease in the cocarboxylase content of the heart muscle. Starvation produces bradycardia, either alone or during thiamine deficiency (29). Potassium, but not thiamine, deficiency produces myocardial necrosis in rats. Animals fed diets deficient in both thiamine and potassium showed no such lesions. The reason for this paradox is obscure (30). Since the bradycardia of thiamine deficiency in rats disappears when the auricles are isolated, it is probably of neurogenic origin (31). Thyroid feeding does not produce tachycardia in thiamine deficiency in dogs; but with a high vitamin-B diet, the tachycardia persists for only eighty to one-hundred days, the rate then falling toward normal (32).

Necrosis of muscle fibers and replacement by fibroblasts was observed in the hearts of rats after repeated injections of desoxycorticosterone acetate. These lesions were similar to those produced by diets low in potassium, though no clear evidence of potassium reduction was found. However, no heart lesions appeared after the addition of potassium chloride to the drinking water (33). The

administration of desoxycorticosterone acetate (100 to 330 mg. in daily intramuscular doses of 20 to 50 mg.) to eleven healthy students and to one asthmatic student led to increased cardiac diameters of from 4 to 17 mm. (av. 6 mm.) in nine cases, and to marked lowering or inversion of the T waves in two cases and slight lowering in most of the others (34).

Frog hearts, immersed in a well-oxygenated, buffered saline solution containing *l*-ascorbic acid (1:10,000), stop in systole within one to two hours because of the accumulation of hydrogen peroxide which is probably formed by the dehydrogenation of the molecule, traces of copper acting as a catalyst. Serum albumin or sodium diethyldithiocarbamate, by inhibiting the catalyst, prevents the systolic arrest (35).

Pathological and other changes induced by digitalis.—Lesions in the cat heart, following the injection of a calculated 60 per cent of the minimum lethal dose of digitalis appeared only after five or more days. Both this dosage, given at one time or in fractions, or even 80 per cent of the minimum lethal dose, failed to produce lesions in all individual cats. Old animals, though free from arteriosclerosis, were more susceptible than young ones. The lesions were focal in distribution, and more common in the papillary muscle and left ventricular wall than elsewhere (36). In hyperthyroid cats lesions were found even after therapeutic dosage. Findings reported in another paper indicate that in rabbits thyroid feeding alone, to the point of emaciation and cachexia, produces as marked histological changes in the heart muscle as combined thyroid feeding and digitalis (37). Toxic doses of digitalis also produce degenerative changes in the central nervous system (38). With therapeutic digitalis dosage, the electrocardiogram showed either no change, or an increase or decrease in height of the T wave, the latter sometimes amounting to inversion. Toxic doses sometimes produced no significant change in the EKG, or changes similar to those due to therapeutic doses. In all but two of these cases there were no myocardial lesions. Changes of a kind which indicate recent myocardial injury in man were consistently associated with demonstrable lesions. The EKG reverted to normal upon healing of the myocardium, with fibrosis (39). Other careful studies are reported of lesions produced in dogs' hearts by toxic doses of digitalis (40); and it appears that atropine exerts a strong protective action (41).

In the heart-lung preparation, therapeutic doses of a digitalis

glycoside (Lanatoside A, B, or C) produced a small, but apparently significant, increase in serum potassium, whereas toxic doses caused a large increase during the period of increased cardiac efficiency. The source was evidently the heart muscle (42).

In normal subjects the cardiac glycosides, Lanatoside C, digoxin, and digitaline Nativelle, produced essentially the same effects, which, aside from the electrocardiographic change, were a prompt, moderate decrease in heart rate of vagal origin, a small rise in arterial pressure, a slight increase in stroke volume, and a slight or questionable decrease in minute output (43).

Earlier reports indicating that the emetic action of digitalis is not due to afferent impulses from the heart are confirmed in careful dog experiments (44). Studies of the clinical action and standardization of the digitalis glycosides cannot be reviewed here (45 to 50).

The mechanism of digitalis action.—Heart failure may be defined as a decrease in the mechanical efficiency of the ventricular muscle, associated with dilatation, a rise in venous pressure behind the failing chamber, and a tendency toward a decrease in the minute ventricular output (51). As the ventricle dilates there is an increase in its oxygen consumption, and this occurs even when the oxygen supply to the muscle is low (52). The digitalis glycosides, as was earlier demonstrated, increase that fraction of the total expended energy which may be utilized in the performance of work, and this apparently occurs even when there is no change in the diastolic volume. This fact was confirmed in experiments on patients (52). Using the Keys and Friedell formula for estimating stroke output from the roentgenkymogram, the authors reported the effects seen one and one-half to two hours after the injection of a solution containing 1.6 mg. of lanatoside C for ten patients with heart failure. The minute and stroke outputs were significantly increased in seven patients and reduced in one, the decrease in the other two being insignificant. The diastolic heart volume was somewhat smaller in four cases. Heart rate changes were insignificant in eight cases, slower in two. On the safe assumption that oxygen consumption is proportional to diastolic volume, it was calculated that the mechanical efficiency increased by at least 37 to 138 per cent in eight cases, with inconclusive changes in two. Study of eight of these patients from three weeks to thirteen months later, after treatment and compensation, dem-

onstrated increased output in five and decreased output in three; and it is, therefore, emphasized that the changes occurring immediately after treatment must be studied if the clinical effect of digitalis is properly to be gauged. In all but one case, however, the diastolic heart volume was significantly smaller than before treatment. The absence of more striking early changes in ventricular volume may possibly indicate that this change is not the primary one in initiating the increase in efficiency; but rather that the volume change is a consequence of the greater efficiency [however, the findings of Bozler (83) should be considered]. These human experiments confirm for man the results of dog experiments, carried out with the heart-lung preparation, in which failure was spontaneous or was induced by chloroform, chloral hydrate, alcohol, or diphtheria toxin, and in which the calculated efficiency was based upon measurement both of work and oxygen consumption (51). Digilanid C reversed the changes associated with failure. Digitalis reduces the mechanical efficiency of the normal human heart.

Drugs other than digitalis.—At moderately low temperatures the heart of the commercial clam, *Venus mercenaria*, is extraordinarily sensitive to acetylcholine, namely, negative inotropic effects appear at concentrations of from 5×10^{-12} to 5×10^{-11} ; and its use in assay is proposed (53).

Acetylcholine (plus physostigmine) does not change the rhythm or strength of contraction of the spontaneously beating turtle ventricular strip, whereas epinephrine and ephedrine produce an increase in contraction amplitude, which is small in comparison with the effect on the atrium or frog ventricle. Automaticity of the ventricular strip is stopped by small potassium excess. Calcium excess strengthens both atrial and ventricular contractions (54). In a study of the action of epinephrine, acetylcholine, and potassium upon the isolated sinus-atrium preparation of the dogfish, *Squalus acanthias*, it was shown that the tissue was relatively insensitive to acetylcholine, but the beats were weakened by 1:500,000 dilutions after prostigmine. The inotropic effect appeared with lower concentrations than the chronotropic [see the paper of Bozler (82)]. Epinephrine antagonized the effect of excess potassium. In spite of the absence of a sympathetic nerve supply, both the untreated and atropinized atria were very sensitive to epinephrine (55).

Single 0.6 gm. doses of quinidine sulphate were found to have little effect on sinus tachycardia in five patients. There was either no effect on heart rate, or a slight increase; and no change in the P-R intervals. One patient developed transitory right bundle-branch block two hours after taking the drug, and this was again observed in this patient two weeks later (56). A soluble quinidine preparation is described for intramuscular injection in the treatment of acute cardiac arrhythmias (57). A toxin in the eggs and embryos of the amphibian, *Triturus*, when perfused through the frog heart, caused first A-V, then S-A block, and later loss of contractility. On washing out the poison, recovery progressed in the reverse order (58).

Disturbances of the cardiac mechanism.—The effect of drugs upon the susceptibility of the ventricles to fibrillation has received further study. In dogs epinephrine was found temporarily to raise the threshold for fibrillation induced by application during the vulnerable period (late systole and early diastole) of a brief and sufficiently strong, direct current. Papaverine hydrochloride and quinidine sulphate has a more lasting protective effect (59). Raising the threshold to externally applied stimuli may not be the same thing as protection against spontaneous onset of fibrillation. Procaine, 933 F (piperidinomethylbenzodioxane), 833 F (diethylaminomethylbenzodioxane), and quinidine did not protect the cat or kitten ventricles against the ventricular fibrillation induced by administration of digitalis (60). Procaine given intravenously may stop, or prevent the initiation of, atrial fibrillation induced by faradization of the atria or by application of mecholyl (61).

Following coronary occlusion, ventricular fibrillation frequently supervenes in dogs and seems to be initiated by an accelerating series of ventricular ectopic beats which originate at or near the boundary between the ischemic and normal muscle. These beats are probably multifocal, and do not always lead to fibrillation (62). Because of the appearance of oscillations with a frequency of thirteen to twenty-five per sec., like those observed when fibrillation is induced by application of a constant current, it is believed that the mechanism of induction of fibrillation may be the same after coronary occlusion [but compare Bozler's view (82)]. Quadrupling of the height of the chief initial ventricular deflection, recorded by semi-differential (contiguous) electrodes placed near the boundary of the ischemic region was observed. The interpreta-

tion of this as evidence of "electrical activity of relatively great intensity" needs careful consideration. There was early blocking off from the ischemic region of many excitation waves. This latter observation is of importance in the theoretical interpretation of the electrocardiogram of coronary occlusion with myocardial ischemia (105).

Despite earlier authoritative opinions, many physiologists have suspected that the observed duration of the A-V interval is dependent upon something more than simple slowness of impulse conduction in the junctional tissues. In a challenging communication (63) the delay in conduction at the junction is explained in terms of an "excitation time" theory, which is supported by experiments on the turtle heart. The hearts were excised, the ventral walls cut away, and the remaining A-V connection cut to leave a conducting bridge only 2 to 4 mm. wide. By means of electrograms simultaneously recorded by two pairs of differential electrodes, it was shown that the entire A-V delay (exclusive of conduction time in atrial and ventricular muscle) occurs in a zone of tissue at the junction, the width of which is certainly less than 1 mm. When the ventricles were excited to obtain retrograde conduction, the somewhat longer V-A delay appeared in the same zone or region. With depression of conduction, the A-V interval increased, not gradually, but in steps which were simple multiples of the normal interval. Examination both by binocular microscope and electrograms then revealed the presence of two or more narrow zones of delay. These latter are regarded as being normally present in parts of the A-V ring of the turtle. The proffered explanation of the A-V pause assumes that no anastomotic connections exist at the junction between A and V fibers and that excitation of the V fibers occurs, not upon arrival of the excitation wave at the junction, but at a time when repolarization of the A fibers is rapid. In a discussion of the conducting system of the vertebrate heart (64) it is noted that in certain amphibian hearts there is a circular arrangement of the muscle fibers at S-A, A-V, and ventriculo-bulbar junctions, and that the connections between fibers seem to convert the morphological rings into physiological "spirals." To this the A-V transmission delay is attributed. The specialized tissue in the hamster's heart has been studied (65).

The familiar phenomenon of the progressive lengthening of the P-R interval in the Wenckebach periods of partial heart block

was restudied in patients (66). Advantage was taken of a human case of reciprocal beats to study the effect of drugs upon A-V and V-A conduction (67). A case of bilateral bundle-branch block was presented (68). Two cases of heart block, with peculiarities in A-V conduction attributable to a supernormal phase, have been added to the literature (69). Microscopic study has revealed anatomical fiber connections, not only between the branches of the A-V bundle, but also between the main bundle and the septum. A case is reported, with careful histological study, in which both branches were severed by disease but A-V conduction (bilateral missed block) was maintained (70).

Interest continues in the Wolff-Parkinson-White syndrome of short P-R intervals and wide QRS complexes in the EKG, often associated with paroxysmal tachycardia. The evidence is now strongly in favor of the interpretation of the phenomenon advanced in 1933 by Wolferth & Wood. A case is reported of a child who presented the syndrome and who died suddenly in an attack of tachycardia (71). Autopsy revealed no gross evidence of myocardial disease and serial sections demonstrated the presence of three muscular connections between the right atrium and ventricle (Kent bundle). Numerous electrocardiograms were taken over a period of about two years in another case of the syndrome, and the effects of digitalis, atropine, and mecholyl were studied (72). Since, according to the theory, the QRS complexes in this condition are often due to a combination of activation of one ventricle by way of the accessory pathway, with only slightly later activation of the opposite ventricle by way of the A-V connection, digitalis, by slowing conduction via the normal junction should widen the QRS complex; and this was clearly observed. Atropine sulphate, then injected, should abolish this effect, as it did. The other effects reported are consistent with the theory. Another case of the syndrome, with attacks of paroxysmal tachycardia "of supraventricular origin," reveals interesting variations in the EKG (73).

Atrial paroxysmal tachycardia with atrioventricular block is described in eighteen cases, and many interesting features are discussed in detail (74). A second paper describes ten cases in which there was slight alternation in the cycle lengths (75). The possible mechanisms underlying paroxysmal tachycardia are discussed. Reentry by way of one of the nodes is regarded as the most attrac-

tive hypothesis. The father and aunt of an infant with paroxysmal tachycardia were apparently also subject to attacks (76). In reporting two cases of paroxysmal ventricular tachycardia in children, the difficulties in differential diagnosis are thoroughly considered (77). A report on ventricular paroxysmal tachycardia, discusses the theory of their production (78).

By means of myograms from the turtle heart, it was shown that early premature beats of the sinus are usually followed by an abbreviated sinus cycle; that late premature beats are followed by a cycle which is somewhat longer than normal; and that beats of intermediate prematurity are followed by cycles of normal duration. Stimuli applied in the refractory period often lengthened the cycle. The possible relationship between the shortening of the refractory period of the early premature beats and the duration of the following cycle was not considered; nor is there any indication that possible effects of stimulation of the intracardiac vagus fibers was controlled (79). Of particular interest in connection with the analogies or similarities between calcium and digitalis action, or decreased potassium, are observations that ventricular premature beats, induced by digitalis overdosage, are eliminated by the administration of from 5 to 10 gm. of potassium salts; and they often do not return until long after the serum potassium falls to fasting levels (80). It is shown in man that an ectopic pacemaker, like the normal one, may be accelerated by exercise, and that a ventricular ectopic focus giving rise to multiple premature beats may become the sole pacemaker (81).

Automaticity; impedance; excitation.—A real step toward solving the underlying mechanism involved in tissue automaticity is reported in two papers which apply to heart muscle methods previously used in the study of smooth muscle. By means of an oscillograph or a mechanical recorder of potential changes coupled with a D. C. amplifier, records were obtained by derivation from an injured and an uninjured part of spontaneously active muscle strips from turtle or mammalian hearts. Both from the sinus pacemaker and from ectopic pacemakers spontaneously arising in atrial or ventricular strips, the sharp potential change associated with response was preceded by a slower potential fall, the "prepotential"; and this was observed only at or near the locally restricted pacemaker region. Acetylcholine eliminated visible mechanical responses of atrial or sinus strips, but the prepotential

rhythms usually persisted, often at the frequency of the rhythm obtaining before treatment, and never at less than half that frequency. In strips not continuously active, a rhythm consisting of prepotential waves of gradually increasing amplitude may appear and beats may supervene, as Luciani periods, at the end of the rhythmic train; and this sequence is repeated. Or, an induced beat may be followed by a decrementing train of waves, the first one or more of which may cause the discharge of premature beats. Positive after-potentials were observed (82). Weak tonus waves are associated, even in the turtle ventricle, with rhythms in electrical potential. In Ringer's solution, forced contraction of the non-rhythmic tissue is followed by a loss of tonus, which is gradually restored. In a mixture of equal parts of Ringer's and 1 per cent calcium chloride solution, the end of relaxation is slow, and tonus waves appear during this period. These are associated with electrical changes, briefly preceding the mechanical (83). It may be emphasized that in these experiments mechanical change always had its electrical concomitant. Ventricular tachycardia, or single or multiple premature beats were induced by treating the dog's ventricular surface locally with sodium or barium chloride solutions. Warming increased and cooling decreased the rate of a tachycardia; warming evoked bigeminy or tachycardia after the mechanism disturbance had disappeared; cooling suppressed a bigeminy. It is justifiably argued that the disturbance induced in this manner is not a reentry phenomenon (84).

Contrary to the findings in nerve, in *Nitella*, and to a previous study of the heart, but in agreement with previously determined changes in skeletal muscle, it is reported that the electrical impedance of the heart increases during systole. The change begins later than the electrogram and persists throughout relaxation (85).

Stimuli, consisting of condenser discharges with a time constant of about 0.8 msec., were applied to the excised turtle ventricle through silver chloride electrodes. The latency before the appearance of the electrical response, even when the response was recorded from the site of stimulation, was roughly inversely proportional to the intensity of the effective stimulus, and may exceed 50 msec. with weak stimuli. Either cathodal or anodal stimuli evoked responses. The phenomenon of summation of subliminal stimuli was clearly demonstrated, the average effective inter-stimulus interval being about 20 msec., after which there was de-

pression. Anodal stimuli cancel responses due to follow cathodal stimulation, and vice versa, if the cancelling stimuli are not applied too late. Between the moments of stimulation and beginning response, as the authors state, there must be some kind of "intermediary process" (86).

The mean heart rate of newborn rats is stated to be 175.0 ± 44.0 beats per min. compared with an adult rate of 433.5 ± 22.0 (87). Homeothermy is not fully developed in young rats until they are three weeks old. At birth, after exposure to a room temperature of 15°C , for fifteen minutes, the body temperature is 16°C (88). At both thirty and one hundred days of age, the heart rate of tamed rats is lower than that of untamed rats. A sex difference was observed (89). The moderate slowing of the heart brought about by injection of bile salt is mediated centrally, and the salt does not inhibit cholinesterase (90). Resting heart rates of 35 to 38 per min. have been recorded, mainly in athletes (91). The highest ventricular rate ever recorded in a human adult is 310 per min., some fever being present (92).

The stages in the development of automaticity of different parts of the chick embryo heart were studied photographically. The more anterior portions of the heart pass through a stage of automaticity which is later lost (93).

Electrophysiology.—Phosphocreatine is considered as the possible energy source of the action potential (94). The idea that the ventricular T wave of the electrocardiogram is an electrokinetic phenomenon, dependent upon a streaming potential associated with ventricular systole is not a new one, and has been abandoned by some who have looked into the possibilities. In spite of the objections, the theory is again proposed, with evidence which is difficult to evaluate (95).

For those who may be able to follow the mathematical presentation, an application of a Green's function to the electrical problem presented by a tissue covered by a closed polarized membrane should be valuable (96). The author points out that the potential in the solution surrounding the tissue is everywhere the same. Other things being equal, the magnitude of this potential is an inverse function of the surface area of the solution in which the tissue is immersed, and reaches zero when the solution is diffusely grounded. It is stated that by the method, "practically all of the discussion of the 'dipole' hypothesis (Wilson, Macleod, and

Barker, 1933) can be put on a rigorous mathematical basis." In apparent disagreement with this mathematical conclusion are the results of experiments with concentric, metal rings immersed in a volume conductor (97). From the results of experiments in which each ring was split into two segments, at different potentials, it was concluded (100) that the change in potential of an injured muscle surface, relative to the potential of a lead-pole placed at a distance in the conducting medium, from negativity in diastole to positivity in systole (the injury activity potential or iap), can be explained on the basis of the classical membrane theory (97). However, the observation that the positive iap develops promptly when injury is induced early in systole and when the muscle is almost fully depolarized (100), may, perhaps, be taken as evidence against this interpretation. Another paper denies the existence of an iap in the dog, because the level of the RS-T segment after "injury" by a 0.2*M* KCl solution is the same as the base line of the EKG when an insulator prevents the injury current from affecting the limb leads. The RS-T displacement is, therefore, interpreted as representing a simple disappearance of the current of injury (98). In view of the unanimity of the reports of those who have observed the iap when injury is more complete and the experimental conditions better controlled, this conclusion may be taken with caution.

A paper dealing with the electromotive forces as vector quantities is immediately applicable in any discussion of the electrical changes associated with the heart beat as recorded in the limb leads (99).

The potential changes at the surface of the dog and turtle heart (with one illustration from *Limulus*) were recorded by unipolar and differential derivations, both without and with injury by the suction electrode method (100). The peak of the differentially recorded curve, without injury, very nearly coincides in time with the onset of fractionate contraction near the electrode, and this peak also coincides with the steepest portion of the movement toward negativity ("intrinsic") of the unipolar curve and with the mid-point of the initial limb of the monophasic injury curve. It is emphasized that the form of the monophasic curve from the same and from different animal species is very similar, that, unlike the normal curves, it is very similar in different regions of the same heart, and that the onset of the monophasic curve precedes the fractionate contraction by a nearly constant interval in differ-

ent ventricular regions. It is therefore argued that the monophasic curve "may be considered, in large part at least, as independent of the potential changes which occur under normal conditions in the surrounding muscle." The authors also confirmed their observation, reported earlier, that during systole the injured surface of the ventricle becomes positive relative to the potential of the resting muscle (iap). Another report agrees that the monophasic curve predominantly reflects the potential changes at the electrode over the injured surface (101).

In apparent contradiction to the foregoing conclusions are studies of the electrogram of the turtle's ventricle recorded with either one or both lead-poles to a cathode-ray oscillograph placed upon the strip or the intact muscle in air (102). In disagreement with the best results of other investigators, these authors find that the monophasic (called monotopic by them) curve recorded from injured-uninjured points is a complex containing no less than four components, represented by seven positive or negative deflections which they number in sequence. In arriving at their conclusions, they neglect the behavior as a semi-volume conductor of the muscle in air, and the reviewer believes that most of their numbered deflections are, in effect, artefacts. Their other results, which cannot be given in detail, do not prove that the lead-pole on the injured surface undergoes little or no change in potential.

An important paper interpreting the electrical changes occurring in ischemia or recent infarction of a part of the ventricular wall points out that the muscle which has died (or is about to die) is intramural; that the subendocardial muscle does not ordinarily die, and remains relatively normal; and that the epicardial muscle layers, external to the infarct, are often so deeply depressed by ischemia that they may be called injured. The intensity of polarization of the injured muscle is decreased. The polarization of the bordering, moderately ischemic, zone is normal, but repolarization is slow after response. It is shown how the endoepicardial orientation of the zones produces the observed RS-T segment shift of the electrocardiogram, and how the slow repolarization of the injured zone during its recovery via an ischemic stage, accounts for the deeply inverted T waves recorded from the chest wall opposite the infarct (103). Of particular interest in connection with the paper just cited are the well-attested reports of T wave changes of the typical so-called coronary type, which followed long paroxysms of

supraventricular tachycardia in otherwise apparently healthy persons, and which reverted fully to normal only after days, or even two weeks (104, 105). The question which arises is, do these T waves, of apparently ischemic type, indicate a persistent ischemia, long outlasting the paroxysm, or are persistent chemical changes without ischemia responsible?

Advantage was taken of exposure of the human heart at operation to study the electrical changes of the human heart through the pericardium. The indifferent electrode was placed on the right forearm. Three curves were simultaneously recorded, one being Lead II, for reference. In one patient, the exploring electrode was placed successively at a point over the right ventricle, and at five points over the left ventricle. In a second patient, three right ventricular and two right atrial points were tested (106). Though the data are scanty, they tend to demonstrate that the sequences of surface activation in man are very similar to those in the monkey, and not unlike the sequences in the dog or cat (107).

Electrocardiographic changes in the limb leads have been studied under various experimental conditions. In one paper are reported the effects of piecemeal cutting away of anterior and posterior parts of one or both free ventricular walls (108). The reviewer feels that too many conclusions are suspended upon too tenuous a thread of procedure, observation, and interpretation.

Complete occlusion of one pulmonary artery, or over two-thirds occlusion, in the dog with closed thorax produces (a) depressed RS-T segments or inverted T waves in the limb leads; (b) elevated RS-T segments and high T waves, and usually a lower R wave, over the right side of the chest; and (c) depressed RS-T segments and sometimes inverted T waves over the left chest. Approximately opposite results follow sufficient constriction of the aorta. These changes were unaffected by cutting or by stimulating the vagi. The circulatory effects of the clamping are discussed. The changes are attributed to damage of the ventricle in question (109). Electrical alternation may persist in the empty dog heart, and is attributed to the heart's "bioenergetic condition (alternans disposition)" (110). This seems to beg the question. A temporary alternation was also noted in the Q-T interval and in A-V conduction time.

When normal persons are placed upon a tilting table, and passively changed from a horizontal to an upright position, a

certain percentage faint within ten to twenty minutes. On change of posture to upright, the P wave usually increases in height; the P-R interval decreases; the mean electrical axis of the QRS complex usually deviates to the right; and the magnitude of the ventricular gradient progressively decreases, to less than 40 per cent of the control value in some instances, and is deviated either to the right or the left. In nearly all subjects the T wave decreases progressively, particularly in Leads II and III, often becoming inverted in Lead III and even in Lead II in some persons. In some cases, the RS-T segment is depressed by more than 0.10 mv. On return to horizontal, the EKG usually returns promptly to its original form, though some T wave change may persist. Some degree of correlation is found between the magnitude of the slowly developing T wave changes and manifestations of sympathetic over-activity, which is most marked in fainters (111). In part these findings were confirmatory of older observations, and are investigated from a different angle in another study (112). The duration of the Q-T interval of the EKG is found to be prolonged slightly in cardiac hypertrophy, and still further prolonged with failure (113). Potassium (15 to 20 gm. of equal parts of the chloride and citrate in 250 c.c. of water) given to human subjects increased the serum potassium and exaggerated the T wave abnormalities due to myocardial infarction, but restored toward the normal, both the abnormal T waves in cases of ventricular hypertrophy (114), and also the low or inverted T waves in thyroid deficiency (115). The use of these effects in differential diagnosis is suggested.

A case of traumatic diffuse pericarditis unassociated with other myocardial damage is described which revealed a typical electrocardiographic configuration (116). A study of the effect of digitalis on the RS-T segment of the electrocardiogram of cats after coronary artery ligation finds that ouabain, like pitressin, increases the extent of the RS-T deviations. Since the electrical effect of ouabain is analogous to that of the known vasoconstrictor drug, it is argued that the former constricts the cat's coronary arteries (117). This effect of ouabain can be duplicated in man, and it may be that the electrocardiographic change is due to a direct muscular effect, which causes blockage of the excitation wave in the depressed muscle and consequent RS-T deviation, rather than to coronary constriction and augmented myocardial ischemia.

The Einthoven triangle.—The year has seen two proposals for

the introduction of new systems of electrocardiography, both believed to be justified by putative deficiencies in the standard routine. Both suggestions follow earlier papers, reviewed in 1943. The one author accepts the absolute validity of the principle of the Einthoven triangle, and proposes to substitute the "augmented extremity leads," together with a common terminal precordial lead. He reports his findings in various clinical cardiac conditions, shows the effects of digitalis, and adds an appendix explaining the relationship between his leads and the standard leads (118). The authors of the other paper reject the Einthoven triangle (119). To the "extra-apical" and C_1 patterns, previously described (120), they now add a "diaphragmatic pattern" of potential change. They suggest substituting leads in which the right scapular region, which they believe undergoes little change in potential during heart activity, is coupled successively with precordial and other regions.

In one of the important electrocardiographic contributions of recent years, it was demonstrated, by methods which cannot here be reviewed, that the specific resistances of the various living mammalian tissues *in situ*, under normal conditions, are so small that they introduce no more than a negligible error into the application of the principle of the Einthoven triangle (121).

Two other papers have given new evidence that, in relation to the muscle masses, the resultant electromotive forces developed during cardiac activity differ less from person to person than the variability of the limb leads might suggest. A comparison of the electrocardiograms and of the x-ray plates indicates that there is a consistent relationship between the spatial mean QRS and QRST axes and the longitudinal anatomical axis of the ventricles in normal persons. It is believed these observations may facilitate the quantitative approach to electrocardiography. The relationships are difficult to understand if the Einthoven triangle principle is wholly invalid (122, 123). Another study, on the basis of the known results of animal experimentation, attempts to discover the cardiac regions responsible for the production of the successive instantaneous axes of the QRS loop of the vectorcardiogram, and concludes that, if the description is correct, the directions of the electrical vectors indicated by the triangle must be very nearly their true directions, as projected onto the frontal plane of the body (124). Evidence pointing in the same direction is to be found in an earlier important paper (125).

The three limb leads of the EKG were taken in the dog while constant currents were passed momentarily through the ventricles in various directions determined by passing rods through the heart or by x-ray plates. The results appear to agree as well with the principle of the Einthoven triangle as might be expected in the dog. The authors' conclusion that the results tend to confirm their previously reported interpretations of the EKG is not a necessary one (126).¹

Precordial electrocardiograms.—In the new-born infant the precordial electrocardiographic CR₂ lead from over the sternum is said to be like that in the adult (R being equal to or less than S). In nine of thirteen cases, CR₆ (over the left ventricle) was like CR₂ in the adult (R being less than S), but in three cases a Q wave was present. In general, during the first few weeks of life, the CR₆ lead developed in the adult direction. The T wave, low at birth, became progressively higher (127). The influence of the indifferent electrode upon the precordial EKG was studied. When Wilson's central terminal is used as the indifferent electrode, its potential changes are considered to be small (128). Certain new, and also hitherto proposed, chest leads have been studied in a large series of normal persons and cardiac patients, but without convincing evidence that they are superior to other derivations more frequently employed (129). Two other papers dealing with chest leads, which do not lend themselves to summarization (130, 131), are of physiological importance, though oriented toward clinical application, and should be consulted by close students of cardiac physiology. A second supplementary report has been made by the Committee of the American Heart Association for the Standardization of Precordial Leads (132).

Clinical electrocardiography.—A Committee of the American Heart Association on the Standardization of Electrocardiographic

¹ Also of interest are careful studies of 97 normal dairy cattle which reveal large differences between the bovine and human limb-lead EKG. These are largely attributable to differences in the intracardiac conducting system in the two species and to the different position of the heart relative to the derivations [Alfredson, B. V. and Sykes, J. F., *Journal of Agricultural Research*, 65, 61-87 (1942)]. An excellent study of the EKG in bundle-branch block and in ventricular hypertrophy gives a useful description of the precordial leads; and a formula is given in another paper for determining the QRS axis by means of unipolar derivations for the extremities [Sodi Pallares, D., *Archivos Latino-Americanos de Cardiología y Hematología*, 12, 135-62 (1942) and 13, 89-100 (1943)].

Nomenclature has issued its report (133). A conservative statement of the place of the EKG in medicine should be useful to the teacher of physiology (134). A clinically useful comparison of the autopsy and electrocardiographic findings in 149 cases is given (135). Electrocardiographic changes are common after cerebrovascular accidents. An example of the changes following hemiplegia, which include bradycardia and cardiac standstill, has appeared (136). Extensive electrocardiographic changes, often including T waves of the so-called coronary type, are reported in Friedrich's disease (137). Autopsy revealed abundant reason for the abnormalities.

Electrically induced convulsions in man produced T-wave changes of the type often observed after severe exercise; certain benign disturbances of the cardiac mechanism were also often observed (138). Study of the electrocardiographic changes after calibrated exercise is stated to offer an improved method for the recognition of coronary disease (139). In patients with coronary artery disease, exercise may often fail to cause abnormal electrocardiographic changes. In many such cases, changes occur if the exercise is taken an hour after eating (140).

Only a few of the studies made of pulmonary embolism, with or without acute cor pulmonale, can be mentioned (141, 142, 143). Dilation of the right ventricle evidently occurs, and the characteristic electrocardiographic changes may be ascribed, in the reviewer's opinion, to the resulting change in the position of the heart, together with delay in activation of the free wall of the right ventricle, when this appears. In addition there are sometimes evidences of damage of that ventricle as in the animal experiment (109), but the extreme human case is rarely graphically recorded. A good resume of the physiological factors involved in producing the changes observed in pulmonary embolism has appeared (143). Changes in the QRS complex of the EKG of ominous significance in pulmonary tuberculosis (144) are thought to be due to rotation of the heart about its longitudinal axis. The reviewer would suggest a transverse axis also. Right axis deviation is said to appear in pulmonary tuberculosis only when there is pulmonary fibrosis (145) and P wave changes are described (146).

On the basis of extensive study, it is claimed that the electrocardiogram is a more reliable indicator of ventricular hypertrophy than is the roentgenogram (147). It seems likely that the electrical criteria of left ventricular enlargement are open to further refine-

ment. One reason why left axis deviation is seen so frequently in hypertension is the hypersthenic build of so many of these patients (148). Electrocardiographic patterns ascribed to combined ventricular strain are described (149); but another study apparently finds few of the type described in conditions which cause hypertrophy of both ventricles (150). Electrocardiographic changes in old age, of a type regarded as abnormal in younger persons, are properly regarded as being due to pathological changes, whether these are relatively benign or not (151). T-wave changes in the electrocardiogram of a type suggestive of coronary artery disease are reported in the hyperventilation syndrome (152). In normal persons, the changes due to forced breathing appear to be non-specific, and may be attributed mainly to the increased heart rate.

Further progress in fetal electrocardiography is reported, one or more satisfactory curves having been obtained in ninety-eight of one hundred cases. The mean fetal heart rate of 148.7 per min. showed no sex difference (153). The clinical usefulness of the method is being established: in showing that fetus is alive when fetal movements and heart sounds are imperceptible; in detection of multiple pregnancy; in differentiating between certain tumors and pregnancy; and, perhaps, in indicating the presentation. It is interesting that neither the sex nor the age of the fetus (after twenty-two weeks before term) has any effect upon heart rate (154).

Congenital defects.—The experimental induction in seven dogs of anastomosis of the aorta and left pulmonary artery, simulating patency of the ductus arteriosus, led to a fall in systemic arterial blood pressure, a cardiac output of the left ventricle which was double that of the right (46 per cent of the blood being shunted into the pulmonary artery), no significant alteration in output of the right ventricle; an increase in heart rate; but no increase in systolic pulmonary arterial pressure (as measured in four dogs). The immediate effects of occlusion of the anastomosis were cardiac slowing, an increase in systemic arterial pressure, and a decrease in output of both ventricles, the decrease being much greater on the left. This persisted for more than a few minutes. Again, there was no significant change in pulmonary arterial pressure (155). The decreased heart rate is attributable to the aortic-carotid sinus reflexes, secondary to the rise in the systemic pressure.

An important study of autopsy findings in 67 cases of patency of the ductus arteriosus is of clinical interest. After age 17, life

expectancy is reduced by 25 years. Hypertrophy of both ventricles or of either one was observed, and was more common on the right (156). Surgical intervention in such cases, together with chemotherapy, often leads to recovery from a subacute bacterial endocarditis, which causes 40 per cent of the deaths (157).

On the basis of study of a mechanical model and anatomical relationships, the dynamics of interatrial septal defect is explained; and it is shown how the superimposition of acquired mitral stenosis (Lutembacher's syndrome) exaggerates the existing circulatory shunt (158). By careful study of cyanosis, physical signs, circulatory dynamics, the EKG, and use of angiocardigraphy, most congenital heart malformations can be diagnosed (159).

Pathological physiology.—The argument as to whether athletics leads to cardiac hypertrophy receives an affirmative answer based upon the comparison of the heart size of 233 athletes with the Hodges-Eyster normal standards; but the conclusion would have been more convincing if there had been a fully comparable control group (160). In rheumatic fever, rapid changes in heart size, due to dilatation, seem to be rare; the increases which may appear progress over months, and recession is equally slow. Large, relatively rapid, increases suggest pericarditis (161).

Distention of the esophagus may cause pain clinically similar to that due to coronary artery insufficiency. Diaphragmatic (hiatus) hernia may at times give rise to such pain, and nitroglycerine sometimes relieves it (162). If not coincidental, the association of paroxysmal atrial fibrillation and disturbances due to hiatus hernia is of interest (163). In another paper five cases of diaphragmatic hernia are reported. In one, temporary T-wave changes appeared in the EKG of a type simulating those often due to coronary insufficiency; and secondary heart involvement, either mechanical or inflammatory, is postulated (164).

The relief of cardiac pain by vasodilating drugs is presumably not merely a consequence of an increased blood flow through the vessels of the ischemic region; it is also due to the diminished systemic pressure and lessened muscle load. In certain cases, the fall in intra-aortic pressure appears to reduce coronary flow much more than local dilation increases it, and pain may result (165).

In normal persons, and in hyperthyroidism without heart disease, the carbon dioxide tension of the expired air varies within a narrow range, the mean being 20.00 mm. Hg. In cardiac patients,

the mean tension varies with the condition. In class II (61 cases) it is 18.55 mm.; in class III (45 cases), 15.81 mm.; and in class IV (32 cases), 13.44 mm., with considerable overlap in the ranges. In angina pectoris the means of a smaller number of patients agreed perfectly with the average of their cardiac classes (II and III). Ventilation was reduced by digitalis. The method differentiates the hyperthyroid obese from the dyspneic obese patient (166).

The blood volume, determined by the method of Gibson & Evans, was increased in all of fifteen patients with congestive heart failure, the average increase being 46 per cent. There were great variability in the degree to which plasma and cells contributed to the increase, a significant correlation between the degree of anoxemia and the increased cell volume, and an excellent positive correlation between heart size and circulation time (167). The rapid infusion of normal saline solution in dogs produced many of the signs of congestive heart failure, including venous congestion, an increase in heart rate and size, and an increase in oxygen consumption (168).

A reduced cardiac output is reported in nearly half of 27 patients in heart failure; and the increased oxygen consumption, averaging 12 per cent, is attributed to the greater muscular work of dyspnea (169). Output is reduced and arteriovenous oxygen difference is increased in mitral stenosis (170).

Methods.—Study of the outlines and the positions of the heart chambers by angiocardiology is said to reveal interesting discrepancies between fact and current teaching; e.g., the pulmonary aorta forms no prominence on the left border; the right ventricle does not occupy the major portion of the cardiac silhouette in the P-A position; and the left ventricle occupies a larger part than hitherto supposed (171). Other papers on the method cannot be listed; a review has appeared (172).

In 147 young men a good correlation was found between fitness, estimated by the study of several physiological responses to severe exercise, and pulse rate at a measured time after exercise; but either no, or no satisfactory, correlation was found with sitting or basal pulse rates, or sitting systolic blood pressure. In normal persons the heart rate in severe exercise may reach 210 or more (173).

A device for the continuous recording of heart rate is de-

scribed (174) and some of its applications, including comparative studies of the toxic effects of digitoxin and ouabain in cats, are reported (175). Interesting curves are presented of vibrations, normal and abnormal, recorded by means of the vibrocardiograph, which was previously described. The vibrations are mainly in the low-frequency, inaudible, range and they are timed from the R wave, which simultaneously actuates the cathode ray beam used to follow the vibrations (176).

Other methods include an apparatus for simultaneous cathode ray recording of heart sounds and the electrocardiogram (177); a capacigraph-string galvanometer for simultaneously recording the R wave of the EKG and arterial or venous pulsations (178); and a simple method for rapid approximate measurement of the transverse diameter of the heart (179).

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CONDUCTION AND SYNAPTIC TRANSMISSION IN THE NERVOUS SYSTEM

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In the present review primary attention is accorded to studies dealing with the problems of neural organization rather than to those studies concerned with the fundamental problem of the cellular processes underlying the conducted nerve impulse, for the latter fall naturally into the category of bioelectric potentials to be reviewed in another chapter of this volume. As material for this review, the available literature published during the year ended October 1, 1943, has been selected, although not to the exclusion of relevant material drawn from earlier reports.

Conduction in tracts of the central nervous system.—Several recent papers deal incidentally, if not primarily, with the velocity of impulse conduction in fibers or fiber tracts in the central nervous system. Fibers of the dorsal spinocerebellar tract attain an average maximal conduction velocity of *ca.* 140 m. per sec. (1). Those fibers making up the reticulospinal and vestibulospinal tracts display similar high conduction velocities (2). The maximum velocity of conduction encountered in the dorsal columns averages 70 m. per sec. (1). Fibers of the pyramidal tract conduct impulses at rates varying from 65 m. per sec. to 18 m. per sec., or even lower (3). Harrison & Corbin (4) report that impulses in the spinal tract of the fifth nerve are conducted at rates approaching 50 m. per sec.

In comparing the velocity of conduction in the dorsal spinocerebellar tract and the dorsal column, Grundfest & Campbell (1) point out that the average ratio of the velocities at which impulses are conducted in the two tracts (1.8) agrees reasonably well with the ratio of the diameters of the largest fibers in the two tract areas as extracted from the data of Häggquist (5). Correlation of data on pyramidal tract conduction with that on fiber diameters (6) reveals that the medium velocity and wide range of velocities of pyramidal impulses are related to the medium fiber size and broad fiber spectrum of the pyramidal tract. At this point it should be noted that the pyramidal tract is well populated with unmye-

linated fibers, the activity of which has not yet been studied by electrical recording methods. Precise information on the conduction of impulses in unmyelinated fiber tracts would be a welcome addition to knowledge.

Thus, although it has not been possible to obtain as precise or exhaustive information on tract fiber conduction as that available on conduction in peripheral nerve fibers, it appears in general outline and for fibers of the A group that the relation between diameter and velocity is similar to that which has been found for peripheral nerve fibers, the absence of Ranvier's nodes notwithstanding. It has been noted (7) that the largest fibers in the central nervous system, i.e., the alpha members of the A group, are concerned with postural systems, while the medium and small A fibers subserve cutaneous sensitivity, flexor reflexes, and voluntary motor activity.

Afferent function of the several fiber types and responses to afferent stimulation.—Final proof that the afferent response to passive stretch of muscles is conducted by the group of largest afferent fibers has been presented (8). The afferent limb of the stretch reflex pathway consists of a fairly uniform group of fibers that conduct impulses at a velocity of ca. 116 m. per sec.

Several recent reviews deal with cutaneous sensibility, particularly with reference to pain (9, 10, 11). Gasser (11) points out that the fibers subserving the different sensory modalities are widely spread throughout the various fiber sizes. Pain-producing impulses are carried in both myelinated and unmyelinated fibers. Conversely, fibers of a given type are not concerned with the transmission of a single sensory modality; for instance, delta fibers are important for the mediation of touch and pain, and there are indications that C fibers may serve to mediate cold as well as pain. Hence, with the possible exception of the stretch afferent fibers of muscle, there is no evidence for a unique relation between fiber type and sensory modality, nor is it yet possible to say, for example, that touch and pain are never carried in the same fibers.

An interesting technique for the study of sensation in its various aspects has been introduced by Bishop (12). The method involves the use of high voltage, low current sparks to stimulate skin receptors without deforming the skin, a useful procedure inasmuch as the prick of a sharp fine needle, as is well known, may elicit sensations of touch, cold, or warmth as well as pain (11).

Spots mediating touch or light pressure, touch associated with hair shafts, and prick extending to prickling pain were readily located. Occasional "cold" spots, but no warm spots, were encountered. Stimulation of a prick spot at subjective threshold was not painful, but rather tactile in quality associated with an aura of itch. On strong stimulation a sharp persistent sting was noted. Similar gradation of stimulation of a touch spot resulted in the sensation of a slight tap increasing to "unpleasantness." Stimulation of a hair receptor gave rise to sensation similar to that evoked by bending the hair.

Utilizing repetitive spark stimulation, prick sensation summates to become frank nonvibratory pain without any feeling that a blow has been struck. Repetitive stimulation of a touch spot results in sensation of vibratory pressure or smooth pressure depending upon frequency of stimulation. Hair receptors under similar circumstances give rise to the sensation of something rough being drawn across the hair.

Except at the tips of the fingers prick has a much lower threshold than touch. The long latency of threshold prick suggests a slowly established peripheral process not characteristic of nerve fibers, while the precision with which the prick spots are localized argues for the activation of discrete localized structures. There may be apparent disagreement between the description by Bishop of highly localized prick-pain spots and the failure of Wollard, Weddell & Harpman (13) to find any specialized endings for pain fibers. Bishop suggests the possibility that the varicosities described by Wollard *et al.* might serve as sites of physiological specialization. Alternatively it seems possible that the fact of "double pain" may provide a clue to the apparent discrepancies. As Lewis (10) points out, pain responses must be reinvestigated from the standpoint of double pain systems. In particular, Weddell's (14) ingenious experiment making use of the fact that the area from which pain cannot be evoked is smaller than that from which touch and temperature sensations cannot be evoked after block of a skin nerve should be repeated to provide an unequivocal statement as to whether or not both first and second pain can be appreciated in the exclusive pain area, and if not, which pain flash is obtained.

Pochin (15) has shown that the delay of response to pinprick in tabetics is due to extinction of the first pain response. In these patients reflex withdrawal is not present (10) which fact leads

Lewis to suggest that reflex withdrawal (the flexor reflex) is associated only or particularly with the rapidly conducted pain impulses (i.e. first pain). This conclusion is strikingly borne out by the results of studies in which various afferent fiber groups have been stimulated in cats. Whereas stimulation of C fibers evokes reflex changes in respiration and blood pressure (16), stimulation of A fibers in the range from *ca.* 12 micra down (i.e., the A fibers less those subserving proprioception) suffices for powerful reflex flexion (17).

Adrian (18) has studied the activity evoked within the brain stem as the result of vestibular stimulation. Discharges of single units are either gravity controlled or rotation controlled, responses to vibration not having been found. Gravity controlled responses were obtained from the right vestibular organ by tilting down to the right or by linear acceleration to the left. Effects from gravity controlled receptors were obtained on rotation if the axis was in the body, but not if the axis was in the head. These gravity controlled responses were recorded at the level of the aboral border of the striae acousticae. Rotation controlled responses, recorded further forward at the brain stem at the level of the oral border of the striae acousticae, were evoked by angular acceleration in the horizontal, median, or transverse plane and by deceleration of steady rotation in the opposite sense. It is likely that some workers will disagree with the assumption that the unitary responses obtained by Adrian were recorded from the vestibular nerve fibers entering the nucleus, although it is certain, as Adrian points out, that the discharges examined were closely related to the stimulus.

Galambos & Davis (19) have obtained single afferent fiber responses in the cochlear nerve utilizing pure tone stimulation. Each nerve fiber responds to only a narrow band of sound frequencies. The bands may be of varied width, but from a relative standpoint they are closely similar; for instance, a 700 cycle fiber has a range of plus or minus 10 cycles while a 7,000 cycle fiber has a range of plus or minus 100 cycles. Silent periods after bouts of activity and rebounds were observed. It is interesting that Adrian (18) describes the continuous discharge from rotation controlled receptors while the head is at rest, and that Galambos & Davis (19) find continuous discharge in auditory nerve fibers in the absence of any apparent stimulus. In further studies on spontaneous

discharge of single auditory nerve fibers, Galambos (20) reports that tones outside the "response area" for a given fiber reduce or abolish the activity of that fiber. The same event occurs when a fiber responding to an adequate tone stimulus is subjected to a tone lying outside the response area. Not all auditory fibers behave in this manner. The multiplication of instances in which activity in afferent units is suppressed rather than augmented or initiated by presentation of a stimulus which is adequate in the excitatory sense to other units of the same system indicates that the normal afferent input to the central nervous system frequently may be the product of integrative action at the periphery. Galambos suggests that pitch discrimination may involve such action.

Considerable interest attaches to the demonstration that cerebellar responses follow stimulation of skin nerves or natural tactile stimulation (1, 21, 22, 23). Grundfest & Campbell (1) show that the response is not mediated through the dorsal spinocerebellar tract. Snider (24) finds cerebellar responses to tactile stimulation in the trigeminal field.

Chemical correlates of conduction.—The body of evidence to show that acetylcholine is liberated along the length of some nerve fibers, as well as at their terminations, continues to grow (25, 26, 27). Synthesis of acetylcholine has been observed in incubated solutions of physostigminized saline containing chopped or ground vagus or cervical sympathetic nerves, spinal nerves, or roots (26). Nachmansohn & Machado (28) report finding in brain tissue an enzyme, cholineacetylase, which can synthesize acetylcholine under anaerobic conditions in the presence of adenosinetriphosphate, sodium acetate, and choline chloride. The precise function of acetylcholine in the complex series of events associated with or constituting the nerve impulse will provide discussion for some time to come, possibly until a critical demonstration is provided to determine whether or not the release of acetylcholine is indispensable for the conduction of a single nerve impulse.¹ In their recent summary of evidence leading to the hypothesis of cholinergic

¹ It is apparent on reading the literature that the term "nerve impulse" means different things to different workers. To some the term would be restricted to refer only to the sink of current flow during the spike process; others would include, in varying degree, the whole gamut of electrical, thermal, and chemical changes that occur before the nerve fiber may again be said to have reached its resting state of dynamic equilibrium.

conduction, Fulton & Nachmansohn (29) conclude, "There are certainly other factors and reactions involved in the propagation of nerve impulses, but the new investigations indicate that acetylcholine in any case is an essential link in the generation of the electrical changes recorded during activity." Feldberg (26) claims "There is, as yet, no evidence that the release of acetylcholine, with subsequent synthesis, is necessary for the passage of an impulse in cholinergic nerves." It will be noted that there is not necessarily any conflict between these two opinions. Von Muralt (25, 30) concludes that acetylcholine is liberated from its precursor during activity to be reconverted into this precursor during the refractory period. In a recent paper (30a) Von Muralt discusses further the role of acetylcholine and vitamin B₁ in nervous excitation.

Enzymes catalyzing the breakdown of acetylcholine continue to receive attention. Nachmansohn *et al.* (31) report that volts per cm. and cholinesterase activity are different but parallel at various levels of electric organs, but that the Q_{10} is practically constant from head to caudal end of the organ. Mendel & Rudney (32) find two types of cholinesterase; one, present in serum and pancreas, acts upon tributyrin, and methyl butyrate, even on two thousand-fold purification. Physostigmine has an equivalent action upon acetylcholine and nonacetylcholine hydrolysis by this enzyme, which accordingly is termed pseudocholinesterase in contradistinction to true cholinesterase obtained from blood cells and brain. In extracts from these latter tissue physostigmine distinguishes between acetylcholine hydrolysis and tributyrin hydrolysis, so demonstrating the presence of separate enzymes. Mendel & Hawkins (33) noted the effect of intravenous injection of purified cholinesterase on the pupillary light reflex, and conclude that acetylcholine plays an essential role in transmission to the sphincter pupillae. Herrmann & Friedenwald (34) have examined the cholinesterase content of the chorioid plexus and ciliary processes. Their finding that the cholinesterase content is not significantly different before and after the onset of secretory activity in the embryo is of interest.

Kwiatkowski (35) reports that a substance pharmacologically indistinguishable from histamine can be extracted from nerves, and that the resulting extracts are inactivated by histaminase. Nerves having the property of causing antidromic vasodilatation

have a high histamine content, and stimulation of cut dorsal roots results in the liberation of an histamine-like substance into the venous blood. Lambert & Rosenthal (36) describe the liberation of histamine in skin on stimulation of the splanchnic nerve. Kwiatkowski suggests that histaminergic nerves exist as well as cholinergic and adrenergic nerves.

Synaptic transmission in sympathetic ganglia.—Eccles (37, 38) has examined the potential changes between an electrode placed at the pole of the stellate ganglion and an electrode at the cut ends of the cardiac nerves following curare block of transmission through the ganglion (39). A single preganglionic volley causes the ganglionic lead to become negative relative to the postganglionic lead, the p.d. reaching a summit of 100 μ V within 10 to 20 msec. and later falling exponentially over several hundred msec. This p.d. is referred to as the "synaptic potential" and is likened to the end-plate potential studied earlier by Eccles and his co-workers. On successive stimulation summation occurs, the second synaptic potential being enhanced. As the frequency of stimulation is increased progressive fusion of synaptic potentials occurs, until, at a frequency of 140 per sec., practically no undulation remains. As curarization decreases, the summation of two synaptic potentials results in the initiation of propagated spikes; subsequently a progressively larger spike potential appears with single stimulation until full transmission returns.

The synaptic potential evoked by a single presynaptic volley is not significantly affected by physostigmine. On repetitive stimulation the negativity of the ganglion is prolonged by the action of physostigmine.

In the normal ganglion, the potentials recorded with one lead on the ganglion and one on the postganglionic trunk following a presynaptic volley include the spike potentials, negative and positive afterpotentials, and the synaptic potential. Comparison of responses to presynaptic and antidromic tetanic stimulation reveals that the summated synaptic potential present in records obtained with the use of presynaptic stimulation is absent following antidromic stimulation. Furthermore, physostigmine has no action on ganglion potentials antidromically evoked. When the summated synaptic potential resulting from presynaptic stimulation is sufficiently large, afterdischarges occur, and these are prolonged and intensified by the use of physostigmine.

The synaptic potential has been analysed by Eccles on the basis of Hill's "local potential" theory (40), in order to obtain the time course of the transmitter action. Such analysis indicates the existence of a "peak" action and a slow "tail" action. On repetitive stimulation the peak is smaller, the tail larger and of longer duration. Physostigmine does not alter the peak and tail transmitter actions. The peak action is related to the direct excitatory action of the action currents of the preganglionic impulses. The properties of the tail action suggest that it may be due to a cholinesterase resistant substance liberated by preganglionic stimulation. Eccles proposes the hypothesis that the tail action is due to acetylcholine which is removed by an physostigmine-resistant mechanism such as resynthesis to its precursor, and also partly by diffusion to the barrier of cholinesterase (41). Physostigmine inactivates the cholinesterase barrier and acetylcholine is free to exert a prolonged action. The prolonged depolarization, synaptic potential, and after-discharge result.

A study of Eccles' findings in ganglia blocked with curare and Lorente de Nó's (42) experiments with blocked nerve reveals certain broad similarities that invite comparison. For instance, on repetitive stimulation the spikelike potentials recorded at or below a cocaine block in nerve undergo decrement as do the peak transmitter actions in ganglia. Again the residual negativity described by Lorente de Nó sums on repetitive action in a manner resembling the progressive increase in the tail transmitter action. Furthermore, the concept of peak and tail transmitter actions agrees with the course of "Wedenski" facilitation below a block in nerve. There is, on the other hand, no known parallel in nerve for the prolonged action provoked in ganglia by physostigmine. Since Eccles relates this action to accumulated acetylcholine, and because of recent interest aroused by the presence of acetylcholine in nerve, a thorough and critical investigation of the action, if any, of physostigmine on transmission and facilitation across a block in nerve would seem to be indicated.

The spinal cord and reflex transmission.—Evidence has now accumulated to show that the myotatic reflex is mediated through reflex arcs of two neurons (8, 17, 43). In studying the relation between the reflex discharge recorded on a ventral root and the size of the causal dorsal root volley, it was found (43) that activation of the dorsal root fibers belonging to the upper third of the A

fiber diameter spectrum accounted for all of the known direct actions of dorsal root fibers on motoneurons (the two-neuron-arc discharge, facilitation, and inhibition). The reflex effect attending stimulation of the A fibers of medium and small caliber was transmitted through arcs of three or more neurons in series. Those observations led naturally to the demonstration that two-neuron-arc reflex discharges may be recorded in a ventral root on stimulating muscle afferent fibers, but not on stimulating cutaneous nerve. It has been shown (17) that the two-neuron-arc reflex discharge resulting from stimulation of the afferent supply of a given muscle reflects only into that muscle, and thus has the characteristic distribution of myotatic reflexes (44). Finally studies on the responses evoked by natural stretch stimulation (8) have shown that the afferent response is conducted in the afferent fibers of highest conduction velocity, and that the reflex response is transmitted with but a single synaptic delay.

Reflex discharges transmitted through arcs of three or more neurons in series and resulting from stimulation of medium and small afferent fibers in either muscle or skin nerves (17), or in dorsal roots (45), are largely restricted to the motoneurons of flexor muscles and represent the flexor reflex. The motoneurons of flexor muscles do have direct connections from dorsal root fibers, and two-neuron-arc reflex excitation of flexor muscles is realized. As in the case of extensor muscles the afferent fibers making such connections arise in the flexor muscle itself, and the reflex discharge obtained through these connections represents the flexor stretch or "pluck" reflex.

The flexor reflex proper is usually regarded as a response to nocuous stimulation. Among the afferent fibers the stimulation of which leads to flexion are the largest fibers present in cutaneous nerves, and the question of whether these fibers mediate pain sensation naturally arises. There is, in fact, some evidence that they do; but on the other hand Macht (46) reports a purely spinal reflex of withdrawal to cold stimulation which, in the normal animal, is masked by a tactile withdrawal response dependent upon the functional integrity of the frontal poles. Since afferent fibers mediating cold fall into the upper range of afferent fibers in cutaneous nerves it seems possible that afferent fibers of more than one modality participate in the flexor response evoked by stimulation of cutaneous nerves.

Campbell (47) describes a reduction or loss of two-neuron-arc reflexes in the seventh lumbar segment ten to twenty-seven days after section of the sciatic nerve. Multineuron-arc reflexes were still present. A detailed analysis of the segmental contribution to the gastrocnemius-plantaris and tibialis anterior muscles in the dog shows the former to be supplied largely by the seventh lumbar and first sacral segments, and the latter by the sixth and seventh lumbar segments (48).

McCouch, Hughes & Stewart (49), continuing their studies on the relation between cord potentials as recorded from the dorsum of the cord and reflexes, describe some of the effects of hemisection and subsequent transection of the spinal cord (50). Crossed excitation was more effective from the acute to the chronic side; inhibition from the chronic to the acute side. Only exceptionally, however, was asymmetry reflected in the cord potentials. Tzkipuridze (51) observed that stretching of the m. gastrocnemius or triceps femoris during reflex contraction of a flexor muscle in response to stimulation of the peroneal nerve converts the normally steady contraction of the flexor into a rhythmic contraction. Decerebrate rigidity in the bat is of the flexor type (52); in the sloth it is usually flexor, but may be extensor in type (53), the findings in general conforming with the view that decerebrate rigidity represents the hyperactivity of antigravity muscles.

Transmission in long spinal reflex pathways from forelimb to hindlimb has been examined (54). Activity evoked by stimulation of forelimb afferent fibers extends aborally through ipsilateral (uncrossed), through crossed, and through recrossed pathways. The lateral columns of the spinal cord serve for strictly unilateral transmission, whereas the ventral columns serve for bilateral as well as unilateral transmission. Internuncial activity in the hindlimb segments of the cord follows tract activity and is confined to the ventral horn, being particularly conspicuous in the nucleus of the anterior commissure. Facilitation of motoneurons coincides with activity in the internuncial pools of the ventral horn. Motoneuron discharge in response to long spinal reflex activation is bilateral, but direct inhibition of motoneurons, which begins with the first arrival of tract impulses in the lumbar segments, is apparently confined to the ipsilateral side.

Ozorio de Almeida (55) reports that heat and cold paralysis of the frog's spinal cord result from concentrations of metabolic

products which are ineffective at mean temperatures. While considering the effect of temperature changes on the activity of the spinal cord attention should be directed to a note (56) describing the increase in reflex discharges as spinal cord temperature is lowered from the normal range. It is possible that a slowing of the time course of the excitatory event at the synaptic knobs by cooling results in a more effective stimulation.

Continuing his studies on the effects of temporary asphyxia on the spinal cord, van Harreveld (57) finds that a slight extensor tone develops shortly after the end of an asphyxiation, and lasts for *ca.* 30 min. This is followed by a period of areflexia, but extensor tone can be reinstituted by renewed asphyxiation. After 15 to 25 min. asphyxia, the areflexia is followed by the return of tendon reflexes and recovery to normal. Following more prolonged asphyxia great extensor tone develops, which on passing leaves the cord reflexly unexcitable for the remainder of life. In some cases the secondary extensor tone remains permanently. Some of these effects are ascribed to differential destruction of inhibitory and excitatory structures.

The respiratory complex.—Several recent papers by Pitts (58, 59, 60) on the respiratory complex deserve special mention, not alone for their interest in relation to respiration, but as contributions to neurophysiology. Stimulation of the inspiratory center leads to prolonged discharge of phrenic motoneurons and inspiration. Stimulation of the expiratory center leads to inhibition of phrenic motoneuron discharge. The inspiratory center acting in isolation, i.e., in the vagotomized, low decerebrate preparation, provokes maintained phrenic discharge. In the high decerebrate, but vagotomized preparation the phrenic discharge is periodically interrupted, indicating that activity from the inspiratory center is relayed cephalically and returned to the expiratory center, the activity of which inhibits the inspiratory center drive of the motoneurons. Similarly in the low decerebrate preparation with intact vagi phrenic motoneuron discharge is periodic, the afferent vagus discharge arising in stretch receptors of the lungs serving to inhibit phrenic motoneuron discharge. Accordingly Pitts speaks of (a) the inspiratory center-motoneuron system responsible for "tonic" motoneuron discharge, and sensitive to chemical environment; (b) the vagal inhibitory system, which is regarded as delivering excitatory impulses to the expiratory

center; and (c) the brain stem inhibitory system likewise acting through the expiratory center. Many other details deserving attention are to be found in the original papers. In another paper Pitts (60) has developed the well-conceived experiment of studying the inspiratory center-motoneuron system by the use of single shocks to the center delivered at mid-inspiration and mid-expiration. The functional pathway from center to motoneurons is much shorter at mid-inspiration than at mid-expiration, the measurements unfortunately not permitting an unequivocal statement on the minimal pathway from center to motoneuron. On single shock stimulation of the inspiratory center facilitation of the phrenic motoneurons lasts for some 30 msec., but when the descending inspiratory paths are stimulated facilitation lasts only 5 msec. The inference is that continued delivery of impulses from the inspiratory center rather than spinal internuncial activity largely determines the facilitation of phrenic motoneurons. With strong stimulation of the inspiratory center extensive discharge of phrenic motoneurons ensues and subnormality of those neurons results. The rate of repetitive discharge of phrenic motoneurons, then, represents the balance between excitation from the inspiratory center and the intrinsic recovery of the motoneurons. This analysis is entirely in accord with current concepts of repetitive discharge of central neurons in other systems (cf. 3, p. 531; 61, p. 226).

Action in motoneuron somata.—Attention recently has been devoted to the problems of conduction in the somata of motoneurons. The action potential of the soma has been described by Lorente de Nó (42), and it is hoped that a wealth of new detail will soon be forthcoming. The response of the somata of motoneurons, conveniently evoked by antidromic stimulation, may be facilitated and inhibited, even though the volley entering over the axons remains unvaried (62, 63). Renshaw suggests that impulses are conducted with a decrement over the soma (62, 64), and that the decrement is augmented or decreased by the consequences of activity in premotor neurons. As a result the antidromic impulse would travel less far, or further into the soma. Recently it was found (63) that an antidromic volley did not block a reflex volley unless the two clashed in the motoneuron axons. As the reflex volley fell progressively later the percentage transmission of the reflex volley increased to a plateau after which a further increase took place. The range of intervals between antidromic and reflex

stimulation which yielded constant reflex transmission, i.e., the "plateau" period, had a duration of *ca.* 1.5 msec. These observations were interpreted to mean that reflex impulses in some motoneurons were transmitted subject only to axonal refractoriness, while in others reflex impulses were transmitted only after the somata had recovered from refractoriness. The abrupt discontinuity in the recovery curve was taken as indicating that the antidromic impulses either did or did not enter the somata, i.e., some of the antidromic impulses were blocked at the axon-soma junction. Through those motoneurons in which the antidromic volley was blocked, reflex transmission over the soma would be normal, or even aided by the operation of events known to occur in the region beyond a block (42, 65), and the reflex impulse would be transmitted to the periphery as soon as the axon had recovered from absolute refractoriness. Through those motoneurons in which the antidromic impulses penetrated to the soma, reflex transmission would only appear after recovery of the soma as well as of the axon. It was found that events that increased the soma response reduced the extent of reflex transmission during the plateau period and those that decreased the soma response increased the extent of the reflex transmission during the plateau period.

It must be remembered that the observed alterations in size of the soma potential under experimental conditions do not of themselves reveal the process by which the alterations take place. Therefore, one must rely on other evidence. If the antidromic impulses were to decrement over the somata one might with justification expect to find all intermediate degrees of penetration of the antidromic impulses between complete block and full penetration, with the result that the curve of recovery of reflex transmission would present an extended but relatively smooth contour. The fact that abrupt discontinuities occur with a plateau between them is evidence for the view that the antidromic impulses are either blocked before entering the soma or else penetrate the soma as all-or-nothing impulses.

Inhibition.—Within the past year new examples of direct inhibition have been encountered (66). In addition several recent compilations and discussions of current information concerning inhibition, direct and indirect, are available (7, 67, 68). Renshaw (45) describes inhibition, by a seventh lumbar dorsal root volley, of the discharge of vastus medialis motoneurons in response to a

sixth lumbar dorsal root volley when the two volleys arrive at the cord in virtual synchrony. Of particular interest in Renshaw's paper is his differentiation of the depression of reflex effect resulting from the central actions of antidromic volleys in motoneurons (69) and that caused by orthodromic volleys in afferent fibers.

The facts (a) that direct inhibition of two-neuron-arc reflex pathways results from threshold excitation of a dorsal root (43), under which condition no cord potential is evoked and no motoneurons fire; (b) that the curve relating intensity of inhibitory effect on motoneurons to the size of the causal dorsal root volley is identical to that relating direct excitatory effect (detonator action) of a dorsal root volley to the size of the causal volley; and (c) that both the inhibitory and excitatory curves are single term curves, reinforce the opinion that the depression does indeed result from the direct action of dorsal root collaterals. The mechanism of such inhibition is still obscure.

While agreeing with the statement that the "inhibitory" dorsal root volley must be synchronized with or earlier than the "excitatory" dorsal root volley for inhibition to occur (66), Renshaw (45) lays considerable stress on the fact that an "inhibitory" volley arriving at the cord (dorsum) immediately before the discharge of the tested motoneurons (i.e., somewhat after the "excitatory" volley arrives at the cord) produces no demonstrable inhibitory action, which fact would appear to mean that the excitatory event at the synapse, once instituted, cannot be checked by the subsequent arrival of "inhibitory" impulses. In other words, the inhibitory process, whatever it may be, must begin to act at least as soon as does the excitatory process leading to motoneuron discharge in order to exert a tangible effect.

Following his observations on the depression by the action of epinephrine of response in sympathetic ganglia (70, 71), Marrazzi (72) finds that the "on" and "off" potentials recorded from the optic cortex are reduced by epinephrine injected intravenously. Experiments designed to localize the action of the injected epinephrine are interpreted as indicating that the retinal and either the geniculate or cortical relays or both are loci of effect.

¶ In sympathetic ganglia, Bülbring & Burn (73) report augmentation of impulse transmission by small amounts of epinephrine and depression by large amounts, which does not agree with Marrazzi's earlier finding the small doses of epinephrine and the

sequelae of splanchnic nerve stimulation regularly inhibit transmission through ganglia. Marrazzi's conclusion would appear to have the advantage of stemming from more direct experimental procedure and analysis.

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VISCERAL FUNCTIONS OF THE NERVOUS SYSTEM

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It is interesting to recall that some forty years ago Sherrington (1) included a description of spinal visceral reflexes in a chapter on "The Spinal Cord" which he contributed to Schäfer's *Text Book of Physiology*. In the course of the article he drew attention to the fact that

after destruction of the higher nerve centres, e.g. brain, the competence remaining to the spinal centres is found greatest for visceral reactions. From this point of view the visceral reflexes present the most perfect reactions of the spinal animal. The bulbo-spinal animal, receiving as it does the afferent impulses of the vagus as well as of the thoracic and sacral nerves, may indeed be considered as regards visceral function a fairly perfect animal. The purely spinal animal does, however, exhibit some amount of damage to the nervous regulation of its viscera; this is chiefly of the nature of "shock" and temporary.

Magoun (2) rightly points out that "the full role of the autonomic system in the integration of bodily processes is only exerted through the action of essential supranuclear centres in the medulla, hypothalamus, and cerebral cortex." It should be emphasized, however, that the viscera, though dependent on the nervous system for the integration of reactions and necessary adjustments, are capable of independent function after section of the extrinsic nerves.

It is intended to include in this chapter studies on the representation of the sympathetic and parasympathetic systems in the cerebral cortex, hypothalamus, medulla, and the spinal cord, together with investigations on the autonomic nerves in their more general aspects. Papers concerned with the problem of visceral sensation, including referred pain, will also be discussed, and reference will be made to the viscerosomatic and somaticovisceral reflexes which seem logically to belong to this section.

CENTRES

Cerebral cortex.—Few papers describing the influence of the cortex on the discharge of impulses by way of the autonomic nervous system have appeared during the year.

It is reported that stimulation of the motor focal points on the sigmoid gyrus of the dog, anaesthetized with chloralose, produced a fall of blood pressure and an increase in heart rate. Respiratory movements were usually decreased in amplitude and increased in number. The depressor effect, though associated with muscular movement, was not dependent on it. It was observed that an increase of renal volume accompanied the fall of blood pressure. It is suggested that vasodilatation of the visceral organs was probably the cause of the depressor effect (3). Postmotor foci influencing the gastrointestinal tract and their descending pathways have also been described (4).

Hess & Brügger have found that stimulation of the septum pellucidum and the neighbouring tissue elicited marked signs of emotional excitement in cats. Evidence has also been obtained of descending pathways which connect this region with other parts of the nervous system. The authors suggest that the results reported provide evidence of a centre which coordinates vegetative function and emotional behaviour (5).

Hypothalamus.—A case is reported which throws light on the functions of the hypothalamus in man. The following abnormalities are ascribed to the destruction of this region by a tumour: diabetes insipidus; suppression of functions of the anterior lobe of the pituitary, the thyroid, the ovaries, and the adrenal glands; disturbance of fat metabolism, of sleep, of thermal regulation, and of personality (6).

The influence of the hypothalamus on respiratory exchanges has also been investigated in the cat. Lesions in the middle of the hypothalamus caused a decrease in oxygen utilization and carbon dioxide output and a fall in body temperature. It is suggested that the decrease in the respiratory exchanges is not due to the fall of body temperature. Illustrations are given to show the effects of different lesions (7). A lesion limited to the hypothalamus and basal region of the brain has been shown to abolish the spontaneous electrical activity of the cat's cerebral cortex. The same effect was obtained after lesions of the thalamus or the thalamocortical pathways. On the basis of different kinds of evidence it is argued that the hypothalamus may influence cortical activity through its thalamic connections. In other words, cortical activity is sustained and influenced not only by afferent impulses from the different sensory organs, but also by impulses from lower subcortical levels (8).

Sheehan (9) has reviewed the work on the relationship of the hypothalamus to the large bowel. He comes to the conclusion that stimulation of the hypothalamus usually causes inhibition of movement. A study of experimental hypothalamic obesity in the rat showed that the development of obesity was apparently a consequence of increased appetite and was not accompanied by any fundamental disturbance of metabolism. In some of the animals histological changes were found in both the tubules and glomeruli of the kidney, and in most instances the urine contained albumen and casts (10). Experiments designed to test the hypothesis that the hypothalamus integrates normal sexual behaviour in rats have failed to demonstrate the existence of cells in the medial half of the anterior hypothalamus which have this function (11). Stoll has demonstrated that in cats destruction of the medial hypothalamic nuclei caused changes in body temperature. The adaptation of the animal to external temperatures was also altered. The author suggests that a centre for temperature regulation is situated in this region (12).

Typical nerve cells have been found in the stalk and infundibular process of the neurohypophysis of the dog. The number of cells appeared to be variable in different specimens and in different parts (13).

It has been shown that degenerated fibres, resulting from lesions located in the substantia nigra, ascend to the hypothalamus by way of the homolateral mamillary peduncle. These fibres terminate in homolateral nuclei of (a) the mamillary bodies, (b) the infundibular region, and (c) the lateral hypothalamic area. None of the degenerated nigral fibres appears to enter the contralateral hypothalamus (14).

Mid-brain, Pons, Medulla, and Spinal Cord.—Nielsen found that in eight out of twenty-five cases of verified brain tumour gastrointestinal symptoms were the first signs of the brain disorder and dominated the picture until the diagnosis of brain tumour was made. The gastrointestinal symptoms did not afford an indication of the localization of the brain tumour, although most of the tumours had a near relation to the fourth ventricle (15).

Further attempts have been made to obtain information about thermoregulatory pathways in the brainstem of the cat. The pathways controlling heat loss are found in the intermediate and lateral part of the dorsal tegmentum at each of the levels studied. The

pathways controlling heat conservation are concentrated to some extent in the lateral as opposed to the central portion of the caudal midbrain and pons. In the case of both heat loss and heat conservation the autonomic and somatic activities, namely sweating, piloerection, and shivering, have been observed to be dissociated following appropriate lesions (16).

In the monkey, thermoregulatory pathways for sweating are located in the lateral and anterolateral columns of the spinal cord and exert a completely crossed influence. The fibres cross in the spinal cord close to the level of the preganglionic outflow. Pathways for piloerection and shivering appear to be situated in the anterior column and are both crossed and uncrossed. The main tract is uncrossed (17).

Interesting information has been obtained from a study of six patients on the disturbance in function resulting from lesions in the medulla produced by thrombosis of the posterior inferior cerebellar artery. Selective impairment was observed. Vasoconstrictor responses resulting from cooling of the body were markedly altered. Other functions, such as vasodilatation from heating the body and vasoconstriction in response to sensory stimulation or a deep inspiration, were not affected. Experiments were also performed which showed that vasoconstriction is an active process, while vasodilatation is a passive one caused by inhibition of vasoconstriction (18).

Brenning has described a case in which, as the result of a lesion in the medulla, there was initially total anaesthesia to pain and temperature, and decreased appreciation of touch, below the navel on the left side of the body. After a period sensation gradually returned to the affected region. As the result of numerous measurements of skin temperature on the outer side of both legs made at the same time as short-wave treatment of the brain, the author comes to the conclusion that accompanying an increased temperature of the brain, vasodilator impulses are propagated to the skin vessels. It is stated that the vasodilator impulses are conducted in fibres separate from those of pain, temperature, and touch (19).

The bradycardia produced in dogs with an intact brain as the result of an increase in intracranial pressure has been shown to be dependent upon the integrity of the vagi; and the vagi in their turn are dependent upon neural mechanisms rostral to the medulla. The production of arterial hypertension, on the other hand, seemed to

require the integrity of the medulla and its projections on to the outlying effectors. Neither the efferent nor afferent fibres in the vagus nerves were involved in this effect. The depression of the respiratory function consequent upon increase of intracranial pressure was in itself observed to exert a profound effect in raising the arterial tension and in slowing the pulse rate (20).

Experiments have been made on cats to demonstrate that centres in the medulla influence secretion from the submaxillary and parotid glands (21).

Case histories of five patients have been presented in whom complete loss of sympathetic innervation to various parts of the feet and legs had occurred. It was not possible to localize the lesion (22).

REFLEXES

No change was observed in the peristaltic pattern of the jejunum or ileum in the recently fed or fasting dog following distension of the gall bladder. Inhibition of the activity of the jejunum and ileum was produced, however, by distension of the upper part of the urinary tract of dogs. The effect lasted in most instances as long as the distension was maintained. In some experiments the inhibition persisted for a variable period after the pressure had fallen. Distension of the urinary bladder also caused a decrease in intestinal activity, which was most marked in the lower segments of the intestine. It was also seen that a sudden distension gave rise to a stronger inhibitory reflex than a slow distension (23).

Distension of the proximal colon in dogs usually inhibited the flow of bile from the liver. Inhibition from stimulation of colonic nerves or the inferior mesenteric ganglion was not so frequently observed. As the reflex was excited after separation of the coeliac ganglion from the central nervous system by section of the vagi, splanchnic nerves, and excision of the lumbar sympathetics, it is suggested that the coeliac ganglion is either a true or a pseudoreflex centre for the temporary inhibition of hepatic bile flow which occurs on distension of the proximal colon. The nerve fibres concerned are present in either the thoracolumbar sympathetics or the prevertebral autonomic system (24).

Vasomotor reactions to injury and venous thrombosis in man have been described by Homans. He states that interruption of the sympathetic pathway influences the reaction (25). It has also been

shown that a severe and persistent arterial spasm can be produced in the legs of rabbits by means of a tight wire tourniquet left in place for some hours. The spasm affects the main arteries and also the collaterals of the injured limb. Sympathectomy markedly improved the circulation even though traces of spasm were seen in the main artery (26). Circulatory adjustments during high spinal anaesthesia are reported. About 70 per cent of patients exhibited significant hypotension during operation, whereas less than 25 per cent of the subjects not operated on showed such changes. The fall in blood pressure took place regardless of the type of surgery employed and occurred after the beginning of surgical manipulation in practically all instances. It is pointed out "that the patient whose sympathetic nervous system is extensively denervated by spinal anaesthesia (6th thoracic vertebra or above) is competent from the point of view of the circulation to handle his needs in the resting state in the supine position." Trauma of any sort concomitant with operative manipulation in the face of vasomotor paralysis and loss of vasomotor defence may precipitate a significant reduction in blood pressure (27).

The rabbit is able to compensate to some extent for the effects of gravity (brief tipping experiments) when it is deprived of vagus nerves, aortic nerves, carotid sinus, and splanchnic nerves. Some reflex mechanism, it is suggested, must be responsible for this compensation (28). Edholm has suggested that in the cat the reason for the fall in blood pressure in the feet down position was the collection of blood in the liver, as the fall persisted after removal of the intestines but was abolished after removal of the liver (29).

Vascular changes have been correlated with motor activity and secretion in the stomach of man. The blood flow through the mucous membrane and the motility appear to vary with the secretion of gastric juice. No attempt was made, however, to ascertain the mechanism responsible for these changes (30).

A method of studying viscerosensory reflexes of the uterus and uterine tubes in man by insufflation of the uterine tubes has been described. Definite areas of cutaneous hyperaesthesia were found to be associated with and to depend upon the site of tubal obstruction and the length of the distended portion of the tubal lumen. The areas of hyperaesthesia have been found in general to correspond to the distribution of the pain produced by distension. The hyperaesthesia disappears with the cessation of pain (31).

AFFERENT PATHWAYS

Balchum & Weaver have attempted to investigate the pathways for mediation of pain impulses which follow distension of the stomach in the dog. The results indicated that visceral afferent fibres only are involved; the majority of these fibres traverse the rami communicantes of the eighth to the thirteenth thoracic spinal nerves and enter the spinal cord through corresponding posterior roots. Other fibres enter the spinal cord by way of the rami communicantes and the corresponding posterior roots of the fourth to the seventh thoracic and the first to the third lumbar spinal nerves. A change in respiration has been used as an indicator of pain impulses in these experiments. It is possible, however, that the reflex response may be elicited by impulses other than pain impulses. The results reported agree with those previously obtained with other indicators (32).

Impulses have been shown to enter the spinal cord in dogs as the result of stimulation of a loop of intestine by pressure, heat, mechanical injury, or electrical stimulation of its afferent nerve by way of the dorsal roots from the seventh thoracic to the first lumbar. Most of the afferent fibres do not cross to the opposite side nor ascend or descend in the cord, but make connections with efferent neurones on the same side and in the same segment of the cord. Reflex inhibition of the intestine was used as an indicator. The reflex response was obtained after section of the vagus nerves and removal of the adrenal glands (33).

It has been demonstrated that symptoms of circulatory failure which normally follow bilateral extirpation of the adrenal glands of the dog at a single operation can be prevented by a thorough infiltration with procaine of the sympathetic elements adjacent to the glands prior to operation. The elements involved are the major parts of the coeliac plexus. Afferent impulses do not apparently enter the cord above T1 or T2, as spinal anaesthesia or section of the cord at T1 or T2 affords comparable protection against circulatory failure. Similar circulatory effects follow stripping of the intestine, which can likewise be prevented by spinal section, spinal anaesthesia, or infiltration of the coeliac area with procaine. It is suggested that the reaction is under the control of the vasomotor centre (34).

An interesting observation has been made that stimulation of the lower extremity by pressure, tightening of a tourniquet below

or above the knee, or a strong faradic current in cats with the spinal cord transected between the roots of the second and third lumbar nerves elicited reflex dilatation of both pupils. Reaction was abolished by section of the sympathetic trunk below the second lumbar segment. The same stimuli applied to the forelimb elicited reactions with the roots of the lower five cervical and the first or the first and second thoracic nerves cut. It is evident that afferent impulses can travel from the limbs to the spinal cord by way of fibres in the sympathetic trunks and the rami communicantes (35).

Gordon suggests, as the result of ingenious experiments, that the pressor and depressor reflexes in cats have separate afferent fibres in sensory nerves; the pressor fibres possibly belonging to the C group and having a higher threshold to stimulation (36).

Afferent fibres from the lungs in the sympathetic pathways are stated to have been interrupted at the stellate ganglion and the second, third, and fourth thoracic ganglia for the treatment of asthma. Beneficial effects of the operation are reported (37).

Pain.—A correlation of the visceral sensory threshold with the cutaneous pain threshold has been made in normal subjects. A heat radiation apparatus was used for cutaneous pain and visceral pain sensitivity was tested by distending the lower end of the esophagus with a balloon. A wide range of sensitivity as regards variations in pain threshold and reaction to pain was found. Pain sensitivity appeared to decrease with age and varied with race. There was a significant correlation between cutaneous pain and visceral sensory thresholds (38).

Brown has put forward an interesting hypothesis to explain localization of visceral pain. His view is that the completely developed intestine, long and rotated though it be, and however far parts of it have migrated, is still essentially a midline organ; its nerve supply is that of a short straight tube; its sensitivity is still that of a short straight tube situated in the middle of the abdomen; and it naturally follows that pain produced in a part of that tube, whether short or long, twisted or straight, will be localized in the primary relevant portion of the affected part (39). The biliary pain complex has been analysed and split into five components. These are explained in the light of current theories (40).

A study of the results obtained by section of ovarian vessels and adjoining tissues in the relief of pain produced principally by the

so-called pelvic varicocele is given. Thirty-seven out of thirty-eight patients received complete relief from pain (41). Reference is made later to the absence of pain in labour following presacral neurectomy (88).

Johnson & Boyden have recorded that pain impulses which result from faradically induced spasms of the caecum entered the spinal cord in the cat as low as the second lumbar ganglion, having traversed the superior mesenteric plexus and the least splanchnic nerves (42).

A suggestion that impulses arise from blood vessels of the stomach in man and cause pain has been put forward to explain the phenomena of hunger and pain brought on by ingestion of epinephrine (43). Again acetylcholine has been found to be particularly useful in the treatment of disturbances caused by vasoconstrictor spasm of the arteries of the retina and of the optic nerve in man. It is suggested that relief in painful ocular disease by anaesthesia of Meckel's ganglion is due to interference with nerve fibres, possibly only efferent vasomotor nerves (44).

Experiments designed to demonstrate localization of the sympathetic response in man following the application of a painful stimulus have not proved successful. Left and right index finger volume changes obtained simultaneously, failed to show any difference in amplitude following a unilateral painful stimulus (45).

The records of five patients who were subjected to an intradural section of the upper thoracic roots on both sides for relief of pain in angina pectoris have been published. One patient died following the operation. The other four were alive $4\frac{1}{2}$ years after the operation and had not had any recurrence of pain (46). Two cases of glossopharyngeal neuralgia initiating or associated with cardiac stress, vasodilatation, fall in blood pressure, syncope, and generalized convulsions have been presented. Objective evidence of the blocking of the various components of the response reflex arc was demonstrated by cocaineization of the throat, procainization of the carotid sinus, atropinization of the vagus, and apparently central effects from cocaine acting systematically after its injection into the deltoid muscle (47).

Lewis's monograph, *Pain*, which contains an account of the author's and his co-workers' contributions will be found to be of considerable interest (48).

Efferent Pathways

Pupil.—Evidence has been presented as the result of a study of clinical conditions to show that the Argyll-Robertson pupil may be caused by damage to the peripheral efferent pathway to the pupil. It is pointed out that there are two efferent pathways for pupillary contraction: one serving the light reflex and the other serving the accommodation-convergence synkinesia. It is possible that the fibres concerned in the synkinetic contraction of the pupils on accommodation and convergence run from the third nucleus to the episcleral ciliary ganglia, then relaying to the ciliary body without passing through the ciliary ganglion (49). The effects of stimulation of the preganglionic pathways to the pupil in man have also been reported. Dilatation was produced in the first two individuals by stimulation of the anterior roots of T1; in the third by stimulation of C8, T1, 2, and 3; in the fourth and fifth by stimulation of T1 and 2; and in the sixth and seventh by stimulation of T1, 2, 3, and 4 (50).

Heart.—More information has been obtained of the role of the vagus and sympathetic nerves in regulating the heart rate under various conditions. Observations show that the near basal heart rate of normal nonapprehensive dogs that had been without food for twelve hours and had rested quietly for sixty minutes ranged from 50 to 56 per minute. Bilateral removal of the stellate and upper five thoracic ganglia did not appreciably alter the rate (51). On the other hand Bond has recorded the changes in heart rate of unanaesthetized dogs and cats startled by a short unexpected noise. The cardiac responses from normal animals were compared with the responses from the same animals after various nerves had been cut. In dogs and cats with the sympathetic cardioaccelerators removed and with adrenal medullary secretion excluded, stimulation was promptly followed by inhibition of vagal tone. Cats in addition showed an acceleration which was greater than could be accounted for by loss of vagal tonic influence alone. It is suggested that the carotid sinus was involved in the reaction. Dogs in which the vagi and depressors were cut and medullary secretion excluded showed pure accelerator activity. The effect of respiration on cardiac rhythm is complex and may gradually affect the pattern of response (52).

Observations have been made on the effect of exercise on the coronary blood volume, heart rate, and blood pressure of trained

dogs with denervated or partially denervated hearts. The effects of exercise on animals that had sympathectomized hearts was not essentially different from the results obtained on animals that had innervated hearts. In both series exercise produced increased coronary blood flow, pulse rate, and blood pressure. The effects of exercise were very similar in animals on which complete cardiac denervation had been performed and those lacking only the vagi. Loss of the vagus nerves affected cardiac acceleration profoundly. Vagotomized hearts only increased about 10 to 20 beats per minute with increments of work. This was true whether or not the sympathetic nerves were present. In the absence of marked acceleration and elevation of blood pressure the coronary blood flow was not affected by exercise in animals that had vagotomized or totally denervated hearts; the coronary flow appeared to be influenced chiefly by blood pressure (53).

The effect of atropine on the coronary flow has been studied in trained dogs with denervated and partially denervated hearts. Atropine was without effect on the coronary blood flow, heart rate, or blood pressure of vagotomized animals or animals with denervated hearts. In the absence of the sympathetic nerves atropine caused increases of 25 to 85 per cent in coronary flow and an increase in pulse rate of a similar magnitude. Augmented coronary flow followed the inhibition of vagal tone and was associated with the resulting increased cardiac rate. The increased heart rate was probably responsible for the increased coronary flow following the administration of atropine, but the mechanism by which it is produced was not apparent (54). These results should be compared with those reported by Bond. It is of interest to note that the mechanisms used to produce acceleration of the heart beat appeared to depend on the character of the stimulus.

Cerebral circulation.—Few observations have been made upon the control of the cerebral circulation. One report, however, deals with quantitative measurements of the cerebral blood flow. Stimulation of the cervical sympathetic appeared to produce no significant alteration. The effects of epinephrine varied according to whether intracarotid or intravenous injection was employed (55).

Peripheral blood vessels.—The observation that skin galvanic responses were present in both hands of a patient with Raynaud's disease thirteen days after an extensive anterior rhizotomy had been performed (from T2 to T8 on the right and from T3 to T8

on the left) led to further investigations on the spinal origin of the preganglionic fibres to the upper extremity in man. Of nine cases in which the upper levels of preganglionic outflow to the hand were investigated eight showed the uppermost route of outflow to be T2; in one case T3 was the upper level. In no instance was there any evidence that T1 contained preganglionic fibres which when stimulated caused changes of skin resistance in the hand. Of five cases in which the lowest levels of preganglionic outflow to the hand were observed the various levels found in four cases were respectively T7, 8, 9, and 10, while in the fifth case the level was T8 on the one side and T9 on the other. These observations emphasize the necessity of recognizing the variability of the levels of outflow of preganglionic fibres for the sympathetic control of the upper extremity (56).

Other observations made on patients demonstrated that, following division of the anterior roots on the right side within the dura from C5 to T2 inclusive, vasomotor responses in the arm remained normal. This result is in keeping with those previously mentioned (57). Removal of only the second dorsal sympathetic ganglion is stated to result in as complete sympathectomy, in so far as central connections are concerned, as does the removal of the inferior cervical and upper two dorsal ganglia (58).

Atlas has pointed out that owing to erratic fusion of the lumbar sympathetic ganglionic tissue it is impossible to designate lumbar ganglia on a numerical basis with any degree of accuracy. Observations on man have shown that the sympathetic fibres carried in the third lumbar spinal nerve may occasionally reach as far distally as the foot (59).

It has been known for some time that, after preganglionic section for Raynaud's disease in the hands, evidence of sympathetic activity often returns within a short time, but the mechanism has not been understood. Recent observations suggest, however, that the establishment of new collaterals from severed preganglionic fibres explains the return of nervous control, even as early as ten weeks in man. Experiments on cats showed that functional reorganization occurred, but its exact nature could not be demonstrated. It is possible, of course, that an abnormal humoral mechanism may play a part, but in another series of experiments, carried out by the same investigators, it has been shown that ventral root fibres can regenerate or reestablish connections within

the stellate and superior cervical ganglia (60). Evidence on this point is also afforded by the observations of Brown & Maycock who have demonstrated that stimulation of the peripheral end of the vagus nerve cut in the neck may cause in sympathectomized cats an acceleration of the heart. The effect was abolished when the middle cervical ganglion was paralysed by nicotine. They conclude that the accelerated response to stimulation of the vagus is probably due to the formation of synaptic connections between preganglionic vagus fibres and the denervated cells of the middle cervical ganglion (61).

Other observers have reported, however, that the vessels not only of the skin but also of human skeletal muscle receive vasoconstrictor fibres and possess vasoconstrictor tone. Blocking the nerves to the forearm markedly increased the blood flow in that part, even after the circulation of the skin has been excluded. The effect was abolished in the sympathectomized limb (62).

Injection with novocaine of the sympathetic ganglia supplying the right upper extremity of a normal subject has been shown to cause the same increase in blood flow of the hand as local heat. Inhibition of sympathetic activity is believed to be a sufficient explanation to account for vasodilatation, and there is no necessity for postulating that the sympathetic nerves to the hand contain vasodilator fibres. The fact that either heating the forearm or injecting the sympathetic ganglia with novocaine produced less dilatation than exercise indicated that many other vessels in the forearm were not under the control of the sympathetic nervous system. It is suggested that the vessels of the skin of the forearm are under nervous control and that those of the muscle are not (63).

The response to the vasoconstrictive agent of pain has been tested under different conditions. It was found that neither the basal metabolic rate nor the general peripheral vasodilatation altered significantly the vasoconstrictor response to a pain stimulus in normal subjects (64).

A single induced shock applied to the sympathetic chain (L2 and L3) of cats caused a galvanic current to be given off by the large central pad of the hindfoot. The response was monophasic and had an average latent period of 0.6 secs. and a duration of 5 secs. Shocks at the rate of 2 to 6 per sec. caused completely fused responses. The evidence at hand indicates that the galvanic current produced by stimulation of the sympathetic chain cor-

responds to a change in permeability of the cell walls of the sweat glands as they become activated (65).

Various methods for studying the condition in the vessels when constricted or dilated have been described. The flow patterns in various peripheral arteries are stated to constitute a basis for a qualitative evaluation of differences among flow patterns and of changes in them that are observed with dilator and constrictor drugs (66, 67). Pappenheimer & Maes have reported that a quantitative measure of the vasomotor tone in the hindlimb muscles of the dog can be obtained. The hindlimb muscles of anaesthetized dogs were perfused with defibrinated blood from a pump-lung circulation, while connections with the central nervous system were retained through the sciatic nerve. The pressure and the composition of the blood supplying the limbs were thus independent of changes in the animal. The nervous control of the circulation can be studied quantitatively, and the effects of the nerves on the appearance and viscosity of the blood detected and measured (68).

Evidence has been provided to show that interference with the renal nerve supply does not affect renal tubular secretion, at least with regard to water, colloids, and phenol red. Differences in the rate of excretion of water and of various solutes by the normal and fully denervated kidney were not due to dissimilarities in tubular function, and it is suggested that they must therefore be due to changes in the glomerular circulation (69).

Hypertension.—Studies have been undertaken on the direct measurements of capillary blood pressure in normal and hypertensive subjects to obtain information concerning the nature of the peripheral resistance to blood flow in patients with hypertension.

It has been reported that in normal digital capillaries of healthy subjects and of hypertensive patients vasoconstrictor impulses mediated through sympathetic pathways may be accompanied by a fall in digital capillary blood pressure; the fall, however, was relatively slight. The results also indicate that the digital capillary blood pressure may remain at a relatively constant level during wide fluctuations in digital blood flow (70).

Direct measurements have also shown that the digital capillary blood pressure was qualitatively and quantitatively similar in normal and hypertensive subjects. Reflex vasoconstriction, reactive hyperaemia, reflex vasodilatation, and variations in skin

temperature between 27° and 35° C. produced small changes in pressure; only during increases in local venous pressure did the pressure consistently rise. During vasodilatation (reflex or from local histamine) there was a greater increase in pressure in the venous limb than elsewhere. No correlation existed between digital capillary blood pressure and arterial pressure, except perhaps during histamine hyperaemia; during vasodilatation induced by locally injected histamine (but not in other ways), the capillary pressure of hypertensive subjects exceeded that in normal subjects. In the digits histamine relaxed, to some extent, the increased vascular resistance of hypertension, whereas reactive hyperaemia and reflex vasodilatation did not (71).

By means of the pressure plethysmograph observations have been made on the vascular volume and blood pressure of minute vessels of patients with hypertension and other conditions. The results suggest, as have studies by others of blood flow, that the vasoconstriction of hypertension differs from the vasoconstriction of neurogenic origin (72).

The reaction of intact blood vessels of the fingers and toes to sensory stimuli in normal resting adults, in patients with hypertension, and senile subjects has been examined. The measurements suggest that the reaction time was more rapid, and that the vascular response occurred more suddenly and to a greater degree and was of less duration in hypertensive than in normal subjects. In senile subjects the reaction time was less rapid than normal, the vascular response occurred more slowly, to a lesser degree, and recovery was much slower. No correlation was found between the reaction time and the state of the vascular bed of the part, provided a reaction occurred (73).

In fifty patients with arterial hypertension the responses to graded mechanical stimuli and to local ischaemia of the smallest blood vessels of the skin of the forearm were normal. Of eleven patients with malignant hypertension ten had diminished small blood vessel responses. In five, the small dermal vessels did not respond by reactive hyperaemia to local ischaemia. In thirteen patients with hypertension complicated by a nerve lesion, ranging from a cerebral vascular accident to Parkinson's disease, the small cutaneous vessels were up to eighteen times more sensitive than in the normal or hypertensive groups. It is suggested that the factor or factors responsible for arterial hypertension do not exert

an influence upon the smallest vessels in the benign stages of the disease but must do so in the later malignant phase (74).

During the hypertension induced by paredrinol in subjects with normal arterial pressures, the digital capillary blood pressure remained within normal limits, whether the capillaries were intact, innervated or not. The authors have pointed out that though in several respects the digital capillary blood pressure during hypertension induced by paredrinol was similar to that in essential hypertension, the mechanism of the two conditions is different (75).

Measurements on the effect of renal blood flow and filtration rate made on patients with arterial hypertension before and after bilateral supradiaphragmatic splanchnectomy with lower dorsal ganglionectomy have indicated that the operation did not change the renal blood flow significantly, even when the blood pressure was reduced (76).

The value of sympathectomy in the treatment of disorders of the peripheral circulation has been reviewed by Shumacker. It is pointed out that the good effects which may be expected from sympathectomy can be fairly well assayed by careful study before operation. In the opinion of the author sympathectomy can give excellent results in the treatment of Raynaud's disease and other purely vasospastic arterial circulatory deficiencies; ordinarily the extremities become warm and dry and attacks of vasospasm cease (77). The effects of paravertebral sympathectomy (the stellate ganglia to eleventh dorsal level or below) on circulatory function in essential hypertension have also been observed. Even though the data are not sufficient to justify conclusions regarding the value of this procedure in the treatment of hypertension, yet information of physiological interest has been recorded. The pulse rate and oxygen consumption were progressively diminished during the first six months after the operation; there was little tendency to change during the second six months. Arteriovenous oxygen difference increased during the first six months and decreased during the second six months in most cases. Cardiac output per minute was progressively reduced. Marked postural reduction of blood pressure occurred after the operation, with little or no tendency to recover. The progressive nature of some of these changes is contrary to the usual belief that interruption of nerve pathways causes sudden changes in function (78). The results ob-

tained from the study of fifty-four patients with essential hypertension, who were subjected to surgery of the sympathetic nervous system, have been recorded (79).

Attention is drawn to the effects of injection of an insulin-free, histamine-free pancreatic tissue extract in the treatment of peripheral arterial disease. Gorham & Climenko state that the intramuscular injection of the extract caused a vasodilatation in the limbs and a beneficial symptomatic effect upon patients when vasospasm was a prominent feature (80). Other extracts of a similar nature produced a drop in muscle temperature with no significant effect on skin temperature when injected intramuscularly. When the extract was used for relatively long periods claudication time and "rest pain" were improved. The vascular state of the tissues was not altered (81). More information of the chemical nature and pharmacological action of these substances would be of interest.

Digestive tract.—Experiments on the motor innervation of the colon have demonstrated that the pelvic nerves to the musculature of the colon are cholinergic. It is suggested that unequal distribution of pelvic nerve fibres to the muscle layers and the intracellular ending of certain pelvic nerve fibres explain the discrepancies between the responses of the colon to pelvic nerve stimulation and to injection of acetylcholine. Electrical stimulation of the vagus nerve was ineffective in producing a response. The hypogastric nerves and the fibres of the coeliac root of the inferior mesenteric ganglia which act on the colon were found to be adrenergic (82).

The effects of cutting or otherwise eliminating nervous pathways to the biliary tract have been examined in cats. The experiments indicated that there is no obligatory reciprocal relationship between gall bladder and sphincter since each responded to appropriate stimuli when the nerve to the other was cut. The vagus augments the tone of the gall bladder and inhibits contraction of the sphincter (thereby accelerating the flow of bile); the sympathetic exerts a temporary inhibiting effect on contraction of the gall bladder—a function that is apparently absent in man—thereby retarding the flow of bile from a viscus that is emptying under the influence of hormones and vagal impulses (83).

The control exercised by the nervous system over the alimentary canal in the earthworm and vertebrates has been compared; the similarities are remarkable. The alimentary canal of the earthworm is indirectly controlled by augmentors and inhibitors which

are antagonistic in their effects. In *Lumbricus* the effects of the nerves on the musculature seem to be invariable. In the vertebrates, however, stimulation of the parasympathetic or sympathetic nerves may produce augmentor or inhibitor effects according to the state of the organ (84).

Uterus.—The anatomy of the pelvic autonomic nerves in relation to gynaecology has been considered (85). Hirsch & Martin have also described the distribution of nerves in the adult human myometrium. The abundance of nerves in the body of the uterus and the connections they make with branches of the uterine artery seem to provide the pathways for effecting the control of vascular phenomena. It is of interest to note that Vater-Pacinian corpuscles were found in the crevices of the muscle tissue and more often in the adventitia of branches of the uterine artery (86).

Nicotine has been used to obtain information of the presence of preganglionic and postganglionic fibres in the hypogastric nerves. It was found, that in the uterus of the monkey and of the bitch, nicotine in suitable doses abolished the motor effect of hypogastric nerve stimulation. The inhibitory phase in the monkey, however, was not affected. The evidence suggests that the hypogastric nerves of the monkey contain preganglionic motor fibres and postganglionic inhibitory fibres to the uterine musculature and in the bitch only preganglionic motor fibres. Motor fibres to the uterus contained in the hypogastric nerves of the monkey and bitch are probably cholinergic in nature (87). Small doses of atropine had no effect on the uterine response to stimulation of the hypogastric nerves in the rabbit and monkey. Larger doses (10 to 25 mg.) depressed and often abolished the response for a period. These effects are probably due to action of atropine at the synaptic connections which lie along the hypogastric nerve (88).

A critical evaluation of the long-term end-results of presacral neurectomy has been made. Little disorder of function has been found as the result of an operation which gave an over-all result of 85 per cent relief for primary and secondary dysmenorrhoea following the procedure. It was observed subsequently that labour pains were absent during the first stage of labour in five of the eight patients, and there was absence of pain during the greater portion of the first stage of labour in two other cases (89).

Electrical skin resistance measurements have been used with success to map areas of skin affected by sympathectomy and by other surgical or functional factors (90, 91).

DESCRIPTIVE ANATOMY

The development of the cranial sympathetic ganglia in the cat has been described (92). A detailed examination of the rami communicantes in the rhesus monkey has also been made. It should be pointed out that some form of transverse connection between the sympathetic chains on each side was found in every dissection, but never above the level of the fourth lumbar vertebra (93). Foley reports from a study of the composition of the cervical sympathetic trunk in cats that myelinated axons exceeded nonmyelinated axons. A variable number of nerve fibres remained in the cervical sympathetic trunk after the preganglionic axons had been eliminated (94). The surgical anatomy of the external carotid plexus has also been described (95).

A description has been given by Bergmann of the arterial supply of the human coeliac ganglion and the changes which take place in the vessels with age (96). The characteristics of the human sympathetic ganglion cells cultivated *in vitro* have also been described (97). Histological studies have been made of the afferent and parasympathetic innervation of the lungs and trachea of the dog. A detailed description is given of the variety of endings found in the epithelium of the lung (98). Observations have also been published on the Lacertilian sympathetic system (99).

PHARMACOLOGICAL OBSERVATIONS

Narcotics, especially barbiturates, diminished the salivary secretion elicited through stimulation of the chorda tympani or through injections of acetylcholine, carbaminoylcholine, or pilocarpine (100). The site of the depressant action of barbiturates on the intestine was the postganglionic fibres and muscle cells. The depressant action was abolished by physostigmine. The stimulating action of physostigmine was annulled, however, by barbiturates, thus forming an example of reciprocal antagonism (101).

It has been shown that obstruction of the common bile duct was followed by a marked degree of activity in exteriorized loops of jejunum and ileum during the first two weeks after operation. Subsequently intestinal activity increased but never equalled the normal amount in the jaundiced animal. The decrease of intestinal activity occurred in both the fasting and digesting states. It is suggested that the biliary constituents retained in the blood may be of importance in causing the observed alteration of intestinal activity (102). In this connection the cardiovascular action of the

bile salts with regard to inhibition of cholinesterase is of interest. Investigations showed that bile salt itself, unlike prostigmine, did not enhance acetylcholine, nor is its own action influenced by prostigmine. The characteristic depressor action of bile salt in the circulating blood is not essentially due to the inhibition of cholinesterase (103).

Segments of isolated rabbit's intestine, taken from upper levels of the intestine, were found to be generally more sensitive to acetylcholine, while those from lower levels were more sensitive to epinephrine. It is stated that the difference in excitability to neurohormones is probably an innate property of the muscle fibres which is closely related to the gradient of rhythmicity (104). The effect of vagotomy and of sympathectomy on the sensitivity of the intestinal smooth muscle to epinephrine has been examined. The only denervations which produced marked hypersensitivity of the smooth muscle were those that involved the section of fibres passing to the intestine from cell bodies located in the preaortic ganglia (105). Brown & Wilder have investigated the effect of epinephrine on three human uteri in different conditions. They found that the drug caused a premature contraction which was followed by a compensatory pause; there was no evidence of relaxation (106).

In cats dying of adrenal insufficiency, the splanchnic nerve stimulation or the intravenous injection of pitressin or barium chloride was found to constrict the blood vessels in the splanchnic region, as in healthy adrenalectomized controls. The pressor response to this process in adrenal insufficiency was poor, while that elicited by epinephrine was practically unimpaired. The retention of the pressor effect by epinephrine was attributed to its cardiac stimulating action. It is concluded that splanchnic nerve stimulation, pitressin, and barium chloride caused adrenal insufficiency because the heart failed to respond normally to an increase in peripheral resistance (107). The action of epinephrine, acetylcholine, and potassium has been described in relation to the innervation of the isolated auricle of the spiny dogfish (108).

Anderson & Morris have described the effects of atropine, prostigmine, epinephrine, and calcium on the movements of the fasting human stomach (109). Experiments on the relation of the extrinsic nerves of the intestine to the inhibitory action of atropine and scopolamine on intestinal motility showed that atropine exerted an inhibitory action on the tonus and rhythmic motility

of the intestine independently of the extrinsic nerves. Vagotomy did not decrease the effect but sympathectomy resulted in increased sensitivity of the intestine to the inhibitory action of atropine. The mechanism of the sensitization has not been determined. The most likely interpretation of the mechanism of the action of atropine is that it renders the intestinal smooth muscle irresponsive to acetylcholine which is being produced at a basal level in the intestine independently of the extrinsic nerves. This suggestion implies that the acetylcholine thus produced has a physiological role in the maintenance of intestinal motility. The actions of scopolamine on intestinal motility following the various denervations were indistinguishable from those of atropine (110). It has been shown from a study of tissue culture preparations from the embryo chick heart that a definite relationship exists between the innervation and the acetylcholine content (111). The seasonal changes in the response to stimulation of the turtle's vagus nerves and effects of strophanthin thereon have been described (112).

Emilsson, who has studied the influence of ergotamine on the action of ephedrine and sympatol on the isolated rat's intestine, has found that ergotamine does not affect the inhibiting action of the two drugs. The author concludes that the inhibiting action of sympatol and ephedrine on the intestine is due to direct muscle depression (113).

Lambert & Rosenthal have described a method for the study of skin histamine. It is suggested that histamine may be liberated in the abdominal skin by stimulation of the splanchnic nerves (114).

Attention is drawn to a review which has been published in the *Physiological Reviews* on "Physiological and clinical tests of autonomic function and autonomic balance" (115).

SUMMARY

In this review the writer has drawn mainly on papers which have appeared in American and British publications. The numerous other journals, which would ordinarily have been consulted in addition, were not available owing to war conditions. It is possible, therefore, that a certain number of important contributions has been missed.

During the course of the year more information has been obtained of centres which influence and control the discharge of im-

pulses by way of the "autonomic nervous system." Tracts have been described and it has been possible to separate them in the brainstem.

More visceral afferent pathways have been defined, and it has again been demonstrated that impulses from a viscus enter the cord by way of a large number of dorsal roots. Observations also show that impulses from the limbs may travel to the spinal cord with the sympathetic trunks and rami communicantes. An interesting suggestion has been advanced to explain the localization of visceral pain.

The efferent pathways have been further explored, and it should be noted that many of the investigations have been carried out on man. The accurate description of the pathways to the limbs is of importance. Evidence has been advanced in support of the hypothesis that sympathetic fibres may regenerate after section and establish connections within the neighbouring ganglia.

It may be concluded that the skin vessels of the limbs are controlled by vasoconstrictor impulses, but opinions differ about the innervation of muscle vessels. Inhibition of sympathetic activity appears to account for vasodilatation, though one investigator states that under certain conditions vasodilator impulses are propagated to the peripheral vessels.

Consideration has been given to the conditions of hypertension in view of the many investigations directed towards the separation of the factors responsible for the peripheral resistance. Further information of physiological importance can be obtained from a study of the effects of sympathectomy.

The influence of the hypothalamus on the activity of the cerebral cortex has been demonstrated and studies have been made of the function of the centres which control the discharge of impulses to the glands and involuntary muscles.

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VISION

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Articles not covered by the previous review and appearing before about September 1943 have been considered here. As was the case last year, papers in English are more adequately represented than those in any other language. The number in English would obviously have been greater had not the publication of the results of a considerable amount of government research been postponed until after the war. Despite the fact that not all publications have been available, the total number of papers is appalling and no attempt has been made to review all, even of those seen. The intention has been to select the more significant contributions, although bias, particularly on the basis of interest, cannot well be denied. A large number of minor elementary reviews have been ignored.

Reviews.—A notable list of books on vision has recently appeared but only one of these falls in the present period, Detwiler's *Vertebrate Photoreceptors* (18). In this it has been his plan to "present an account of the retinal photoreceptors in such a form as to be of value to those who have a general interest in the biology of the retina, rather than the specialist."

INTRAOCULAR FLUID AND OCULAR METABOLISM

Sugar (99) presents an excellent summary of the present knowledge of the origin, circulation, and reabsorption of the aqueous and the relation of these facts to glaucoma. The ciliary body has long been regarded as the source of the aqueous but the mechanism of its origin has been disputed. The aqueous circulates from the ciliary body into the anterior chamber and finally makes its exit through the pectinate ligament and into the sinus venosus sclerae (canal of Schlemm). The rate of movement is about 2 c. mm. per min. which would replace the entire volume in about two hours. When aqueous is removed the rate is greatly increased.

Friedenwald, Buschke & Michel (28) have followed earlier studies on the aqueous by a careful experimental analysis of certain aspects of the process by which water is transferred from the

blood into the aqueous chambers. They state that in the rabbit and guinea pig (and with certain differences in the cat),

the interstitial tissue of the stroma of the ciliary processes contains a group of reducing substances, one component of which has been identified as ascorbic acid (vitamin C). These substances act as a mediating system, facilitating the oxidation-reduction interaction between the stroma cells and the stroma-epithelium barrier. . . . Ascorbic acid is stored in the ciliary stroma, being reversibly bound by an acidophilic component of this tissue.

In guinea pigs on a vitamin-C deficient diet, ascorbic acid disappears from the ciliary body long before any general signs of scurvy develop. In such animals withdrawal of aqueous is followed by a "painfully slow" reestablishment of normal intraocular pressure, whereas in normal animals pressure is restored in ten to twenty minutes and usually overshoots the mark. In the cat the level of the redox potential is such that Friedenwald does not think that ascorbic acid can act as mediator (28).

The evidence seems satisfactory that in the forms studied there is secretion of a simple type in which water is transferred by a "metabolic pump" into the aqueous chambers and that in the rabbit and the guinea pig ascorbic acid is part of this mechanism.

From a thousand cases in which aqueous was withdrawn from normal human eyes, Kronfeld reports the following observations (61). The time required to restore the normal pressure is relatively short; in ten minutes 50 per cent of the original volume is restored and after thirty minutes, 75 to 80 per cent. There follows a hypertensive phase in which the pressure rises markedly above normal and which disappears in about four hours. A slight and inconstant hypotonic phase next appears in some cases.

A link in the drainage route of the aqueous has been emphasized by Ascher's demonstration with the slit lamp of aqueous veins in about one-fourth of the persons examined (1). He states,

Aqueous veins are biomicroscopically visible pathways of blood vessel-like appearance, containing a clear colorless fluid or diluted blood, and intercalated, probably via Schlemm's canal, between the intraocular fluid on one side, and conjunctival and subconjunctival veins on the other. Anatomically, they are connected with, or a part of the intrascleral meshwork.

Cogan & Kinsey have made an extensive study of the physiology of the cornea, the results of which have been presented in a series of papers (11, 12, 13, 58, 59). Two problems connected with

the cornea have long attracted attention. One is the marked transparency of the cornea so necessary to its optical function; such transparency does not seem to be promised by the physical structure of fibers and fluid, nor is it obvious why the sclera of almost identical structure and physically continuous with the cornea is so opaque. The main body of each, the stroma, is indeed almost identical but there are important histological differences. Bowman's and Descemet's membranes come to an abrupt end at the margins of the cornea, the epithelium of the anterior and the endothelium of the posterior surface lose the intimate relation to the stroma which they exhibit in the cornea and no other comparable coverings replace them on the surfaces of the sclera.

According to Cogan & Kinsey the epithelium and endothelium are both impermeable to sodium chloride. The cornea is normally dehydrated and pieces placed in water swell several hundred per cent becoming at the same time opaque. The sclera swells but little; if dehydrated it becomes transparent. They conclude that the transparency of the cornea is the result of the normally dehydrated state. Exposed to a hypertonic solution (roughly above 1 per cent) on its anterior or posterior surface, the cornea may be kept dehydrated by the outward movement of water through its semipermeable membranes. There is evidence that the tears and aqueous are hypertonic to the corneal fluid but because of the small amounts of these fluids and the difficulty of obtaining them uncontaminated the accuracy of the data is not beyond question. According to this view the fluid in the avascular cornea is derived from the vascular limbus and moving toward the center of the cornea is lost from both surfaces more rapidly than it is supplied, thus maintaining the dehydration that is the condition of transparency. This circulation also serves to supply the minor needs of the low corneal metabolism.

Not only the water interchange of the cornea but also the passage of drugs through the cornea into the aqueous is important. Swan & White (100) on the basis of experimental work state that "penetration of drugs into the normal cornea is not a simple matter of diffusion." The rate of penetration is affected by the polar nature of the drug, the osmotic relations, the hydrogen ion concentration, the concentration of the drug, and, in general, those factors affecting the penetration of plant and animal cells. "The permeability characteristics of corneal epithelium and stroma

differ considerably. Non-polar and highly surface-active compounds penetrate more readily and polar compounds less readily into the epithelium than into the exposed stroma. Therefore injuries to the epithelium increase the penetration rate of polar and surface-inactive compounds. . . ."

Riboflavin is present in the retina in a concentration exceeding that of all other tissues; 50 mg. per 100 cc. has been reported. Various clinical workers have reported a visual disturbance, said to be distinguishable from night blindness, characterized chiefly by poor visual acuity in low illuminations which is promptly relieved by riboflavin. Heiman (46) concludes from experimental work of his own and others that riboflavin is photodynamic, and hypothesizes that it plays an essential role in vision. Admittedly lacking experimental proof, the view is that riboflavin forms with the cones a functional unit similar to that formed by the rods and carotene.

Riboflavin is reported by Pirie to be found in fish eyes exclusively in the retina (87). He speculates that riboflavin may act as a photosensitizer in the fish eye, giving rise by fluorescence to longer wavelengths capable of stimulating the retina.

The high concentration of vitamin C in the aqueous and lens has attracted the attention of a number of workers. Huysmans & Fischer (50) have reviewed the suggested explanations and, finding them inadequate, advance the view that the lens can produce vitamin C and also reduce the oxidized form. The support for this view is largely the fact that after the extraction of the lens the vitamin-C content of the aqueous is found to approximate that of the blood which it normally far exceeds. Experimental evidence, admittedly lacking, would seem necessary to give a satisfactory basis to this and other speculations.

An analysis of the tissues of the eye for iron, copper, zinc, and manganese is reported by Tauber & Krause (101).

RETINAL PHYSIOLOGY

The known observable retinal responses are meagre compared with the profusion of visual sensations but recent years have added encouragingly to our knowledge in the difficult field of retinal physiology. Work on the photosensitive substances and on action potentials within the retina deserve mention.

Photosensitive substances.—The presence of a photosensitive substance in the cones has been claimed by several workers and denied by others on the ground of insufficient or erroneous evidence. Von Studnitz has published two additional papers dealing with this *Zapfensubstanz* (97, 98). From an extract of the whole eye of a snake (*Tropidonotus*) with a cone retina he obtained an absorption spectrum in which, after the addition of two points from earlier data on the turtle, he distinguished three maxima (97). His technic in using the entire eye has been criticized by Granit (38, p. 112). The identification of three modes in a curve based on observations of unknown variability at ten wavelengths in the spectrum is far from convincing. Where, as here, the argument rests on quantitative results the writer is under the same obligation to present evidence on the extent and variability of his data as to give other features of his technic. In the absence of such evidence in the present case the elaborate color theory advanced deserves little attention.

In a second paper (98) he has reported a photometric study of the oil globules (*Zapfenölkugeln*) of the chicken retina. He regards the material of the globules as a light-stable form of the *Zapfensubstanz* from which the light sensitive form is derived during dark adaptation and into which it returns when bleached by light. Absorption spectra of the extract either kept in the dark or exposed under various filters form the basis of a three component color theory. The differences between the various curves are slight and in the absence of statistical treatment it is profitless to discuss the hypotheses.

The droplets first noted by Kolmer in association with the rods have been carefully reinvestigated by Johnson & Detwiler (55). They consider the droplets to be "histological entities which may be identified with retinene." The evidence seems satisfactory. The authors consider the relations of the droplets of the frog's retina to rhodopsin, retinene, and vitamin A and find that the "droplets and retinene are known to have . . . (1) a common site of occurrence [outer segments of rods], (2) lipoidal nature, (3) mutual absence in extreme avitaminosis, (4) a common occurrence in the retinae of animals dark-adapted at room temperature and treated with certain acids and heavy metal chlorides—and, conversely, a mutual absence or sparsity in retinae light-adapted at room temperature. . . . The few droplets seen in light-adapted retinas may

represent residual vitamin A, in addition to retinene, rather than retinene alone."

Retinal action potentials.—Work on the action potentials of the optic nerve, although modern technic has vastly improved the earlier picture, is still relatively barren, an inevitable consequence because these records represent the overall result of a complex process. The attack on potentials nearer the receptor is more promising.

During the past year Granit has extended his earlier work on the frog. The technic is to expose the retina of an eye with intact circulation in an anesthetized animal and record the potentials from a microelectrode placed near the surface. If the electrode is correctly placed a simple record is obtained coming either from one or from a small group of synchronized ganglion cells. In any case the activity is not derived from a single photoreceptor but from a group numbering possibly several hundred and in nearly every case consisting of both rods and cones.

The threshold was determined for ten or twelve spectral localities and the sensitivity of the preparation plotted as the reciprocal of the energy in an equal quantum intensity spectrum. The series of animals studied includes the frog, snake, pigeon, rat, guinea pig, and cat (36 to 40). The plot of the sensitivity of the dark-adapted eye agrees so strikingly with the absorption curve of visual purple as to leave little doubt of an essential relation. "In light adapted eyes . . . the sensitivity curves . . . are of two types: (i) broad absorption bands, here called *dominators*; and (ii) narrow bands, here called *modulators*" (40). From his figures the dominator band has a range of about 100 $m\mu$ at the 60 per cent level and the modulator a width of 44 to 60 $m\mu$. The dominator band of the light adapted eye corresponds well with the photopic visibility curve of the eye.

The modulators are said to fall into three groups having maxima around 580 to 600 $m\mu$, 520 to 540 $m\mu$, and 450 to 470 $m\mu$ in the red, green, and blue. This is somewhat diagrammatic, however; the pigeon and the cat show shifts thought to be due to the oil globules of the former and the tapetum of the latter and some of the curves are incomplete, appearing only as humps on the flanks of the other modulator or dominator curves. In the guinea pig and the rat the dominator is lacking.

Certain features seem well established. The elements recorded

are of different types as regards maximum spectral sensitivity. According to Granit these have no relation to those yielding the three types distinguished by Hartline as "maintained," "off," and "on-off." That one of the dominators is dependent on the properties of visual purple seems clear. The modulators are less well defined and it is too early to speculate on their correlates. Meanwhile we may await more data from Granit's energetic hands and confirmation from other workers.

Adaptation and vitamin A.—The discovery of a relation between vitamin A and dark adaptation led to a plague of surveys and of gadgets. Most of the surveys and adaptometers were made by men lacking knowledge in one or more of the three fields involved: physical, physiological, and psychological.

Thoughtful and competent statistical analysis of the sources of variability in such measurements has recently been made by Hunt & Hayden (49). Using the adaptometer of Hecht & Schlaer, experienced operators determined the light threshold after various times in the dark. In 63 men and 23 women from low income groups, half of whom received vitamin A during the six weeks of the test, they found no significant difference in the threshold of those receiving, over those not receiving, vitamin A, although in some cases therapy was continued for as long as six months after the tests. There was a significant difference in the average threshold with age. The variability of the thresholds was analyzed and it was found that with repetition of the test the threshold did not change significantly but the observations became less variable. The variability of the observations early in adaptation was greater than later, a fact which finally led them to adopt the 33.5 minute threshold as most stable. From their data and that of other workers it appears that the variability of the observations is, in part, a function of the slope of the threshold time curve; that is, the thresholds are most variable where they are changing most rapidly. This apparently depends upon the fact that if such a curve is displaced in the time axis the band produced is widest in the threshold axis where it is steepest. In the present data the variability shows a correlation of $+0.78$ with the slope of the threshold time curve.

If the total variability is broken down, the largest fraction is that between subjects (64 per cent of the variance), next comes the variability with time of the individual (30 per cent), and last the

variability between a test and an immediate retest (6 per cent).

They conclude "it appears that threshold measurements may be useful and practicable for the diagnosis of night blindness due to vitamin A deficiency in laboratory or clinical or very small scale field investigations but undependable or impractical in studies of a large population group." This has been the attitude of several competent workers and the present findings clearly support it. If some of the early workers had tempered their enthusiasm with a little cool statistics their results would have been notably less striking and more durable.

A study of children by Palmer (85) gave results concordant with those of Hunt & Hayden (49). The light thresholds from the twentieth to the thirty-fifth minute in the dark were measured in 175 apparently healthy children from a private high school near New York. The authors give values of the median and of the pairs of percentiles including 50 per cent of the thresholds and 90 per cent as a measure of variability. They suggest that thresholds of more than $3 \log \mu\text{l}$ at twenty minutes or $2.53 \log \mu\text{l}$ at thirty minutes "are high enough to warrant further study . . . by other diagnostic procedures."

Similar results were obtained by Isaacs, Jung & Ivy (52, 53). A group of 57 medical students tested with the biophotometer gave some indication of effect of diet which, however, was not supported by statistical analysis. The authors do not consider the biophotometer a satisfactory instrument; its variability they have analyzed in an earlier paper and even the revised method of scoring here used shows great variability apparently associated with the early stage of adaptation at which the readings are taken. Three students placed on a deficient diet containing an average of only 74 USP units of vitamin A for over forty days did not exhibit "measurable visible evidence or subjective signs of deficiency" when measured by Hecht's adaptometer. Tests of field size, of blind spot, and of acuity were also negative. Massive doses of vitamin A did not give evidence of improved adaptation. They review previous attempts to produce dietary vitamin-A deficiency and point out the conflicting results.

It must be remembered that not all cases of raised threshold in dark adaptation are amenable to treatment with vitamin A. Congenital night blindness is an example. This aspect is emphasized by McDonald & Adler (74) who give curves of persons with

various ocular defects affecting adaptation such as impaired transparency, chorioretinitis, retinitis pigmentosa, and some cases of reduced light sensitivity of unknown origin. Particularly interesting are those cases in which one part of the retina may show an approximately normal curve while another region shows very defective adaptation. They warn that "dark adaptation tests are of value only if the condition of the eye being tested is first thoroughly investigated. . . . In the present state of knowledge it is entirely proper to say that this [retinal deficiency in Vitamin A] suggests a deficiency of the whole body in vitamin A, but until some correlation has been made between the vitamin A content of the blood and the deficient dark adaptation thresholds such conclusions are presumptive and not proved."

Dan & Yarbrough (16) failed to find such a correlation between dark adaptometer readings and either blood carotene or blood vitamin A in 154 subjects tested with the adaptometer of Hecht & Shlaer. In the abstract available the technic of blood testing is not given. They suggest that the adaptation method is not a reliable way of "measuring mild avitaminosis A, and that the blood test offers a more promising means for determining the vitamin-A status of an individual."

McDonald & Adler (74) found a significant reduction of sensitivity in the case of one man on a vitamin-A deficient diet, but on returning him to a normal diet the sensitivity rose so slowly that the authors warn of the danger of prolonged experiments with hypovitaminosis A. On the other hand poor general nutrition presumably involving vitamin A is not always accompanied by poor adaptation. A twenty-one year old girl with anorexia nervosa weighing only fifty-six pounds was found to have a normal dark adaptation curve.

Oldham and associates (84) report that two groups of children known to have differing vitamin-A intake did not show differing thresholds. Administration of vitamin A caused a slight but significant fall of threshold. From the comparative side Morgan (79) has demonstrated that rats, kept from birth on a diet as low in vitamin A as is compatible with life, have a significantly raised threshold when compared with normals.

Entoptic phenomena.—Entoptic phenomena have been a source of interest and physiological information for many years. Friedman has recently pointed out certain clinical applications and has listed

and discussed a series of the less common phenomena. Those interested are referred to the excellent articles (29, 30, 31).

Pupil.—Wagman and his associates (103, 104) have utilized an ingenious method of infrared photography to record pupil diameter. In this way they have explored with a series of monochromatic light sources the relation of pupil size to light intensity. Data on six men and on the rabbit are presented by Wagman & Nathanson (104) and compared with the earlier figures of Reeves. The range observed is somewhat less than that found by Reeves but the form is similar. Because of the objective nature of the method and the care employed the results seem likely to be accepted as standard. The sensitivity of pupillary response including the location of the maximum in dim light was found by Wagman & Gullberg (103) to agree closely with the scotopic visibility curve for the human eye. They conclude that the pupil size "is under control of fibers activated by the rods of the retina, as well as the cones." Löwenstein and associates in a series of papers (70, 71, 72) describe the technic of pupillography in which the diameter of the pupil is obtained from rapid moving pictures. The normal light reflex, in which the direct and the consensual responses are identical, has the following course. There is a latency of 0.2 to 0.28 sec., although this may be significantly lengthened by fatigue and other physiological conditions, and a contraction phase of about 0.45 sec. which is relatively independent of the time of stimulation. With a stimulus of one second the contraction frequently continues for 0.2 to 0.3 sec. after light has ceased. Both contraction and redilation are most rapid in the initial stage. Löwenstein distinguishes four types of reaction in normal subjects: (a) rapid contraction and rapid dilation, (b) rapid contraction and sluggish dilation, (c) sluggish contraction and rapid dilation, and (d) sluggish contraction and sluggish dilation. He claims that these represent sympathetic and parasympathetic hypotonia and hypertonia. Fatigue is fairly rapidly produced by repeated stimulation.

McCrea, Eadie & Morgan (73) have investigated in dogs and man the mechanism of morphine miosis and conclude that it "depends very largely, but not altogether, on the amount of light falling on the eye, so that the effect of morphine appears to be mainly an exaggeration of the light reflex."

The so-called Stiles-Crawford effect may be stated in the words of Stiles: "that light rays of the same spectral character and physi-

cal intensity entering the eye through different parts of the pupil may produce visual impressions which differ in brightness and colour even though the patch of retina stimulated (the fovea) is kept the same." It is not observed in the dark adapted eye where the periphery is chiefly used. Two loci have been suggested for this effect, the optic media and the retina. In the first it is assumed that light entering the periphery of the dilated pupil suffers greater aberration and scattering than the central beam and hence reaches the retina in reduced physical intensity, the second that rays striking the foveal cones obliquely are less effective in stimulation than the central rays which strike the cones along their axes. Goldmann (34, 35) has recently obtained experimental evidence on the locus of this effect. He used the large Gullstrand ophthalmoscope which both permits the observation of the eyeground and the controlled slit illumination of the anterior portion of the globe. By appropriate optical means he threw on the retina a divided circular field the halves of which were illuminated by rays having different paths, one of which passed through the center of the pupil, the other through the periphery. To the observer viewing the retina through the ophthalmoscope the two half images were of equal brightness but to the subject that half illuminated through the periphery of the pupil was much dimmer. On the basis of this ingenious experiment Goldmann concludes that the Stiles-Crawford effect is a retinal phenomenon.

Visual threshold.—Hecht, Shlaer & Pirenne (45) have re-determined the absolute threshold with great care under the most favorable physiological conditions, "dark adaptation, peripheral vision, small test fields, short exposures, and selected portions of the spectrum." Under these conditions they found that the absolute visual threshold lies between 2.1 and 5.7×10^{-10} ergs in the blue green corresponding to between 54 and 148 quanta at the cornea and 5 to 14 quanta actually absorbed by the rods. This they interpret as representing the absorption of one quantum each by 5 to 14 rods out of the 500 in the geometrical image of the light.

They point out that with so few quanta as are involved at the threshold the stimulus will show marked variation. "It is the stimulus which is variable, and the very nature of this physical variability determines the variation encountered between response and stimulus. Moreover, even when biological variation is introduced, it is the physical variation which essentially dominates the rela-

tionship." The authors deserve credit for calling attention to the inherent variability of the threshold stimulus which has not been fully realized, but their last sweeping generalization is hardly supported by the data. From Table II, page 826, it will be seen that the range is closely twofold. These values were at first obtained by noting that intensity at which observers saw the flash six times out of ten. "Later the measurements were made somewhat more elaborately. Each of a series of intensities was presented many times and the frequency of seeing the flash was determined for each. From the resulting plot of frequency against intensity we chose the threshold as that amount of light which could be seen with a frequency of 60 per cent." The values of the table are thus the sixtieth percentiles graphically determined and, like the mean, do not represent the variability of the individual observations. Furthermore, these observations extended over a year and a half. The method is thus that best fitted to conceal the variability of the stimulus and to reveal the biological variability.

Other observations of a similar nature show larger variations in which the stimulus variability was not accentuated but in which there is a definite basis for a larger biological variability. McFarland & Evans (75) found that exposure to an oxygen pressure corresponding to an elevation of 15,075 feet raised the threshold in dark adaptation over that at sea level for the eighteen observers by an average of 0.3971 log units or a 2.5 fold change. McFarland & Forbes (76) found that the combined effect of low oxygen tension (13.2 per cent) and 4 units of insulin raised the thirty minutes dark adaptation threshold 0.6 log units or four fold. Clearly it is the biological and not the physical variability that is dominant here.

Wald, Harper, Goodman & Krieger (105) have also investigated that aspect of sensory variability due to anoxia. Their findings in part confirm the work of earlier investigators that anoxia raises the threshold of the peripheral dark adapted retina. "Under such circumstances various types of physiological stress cause marked changes in threshold which must originate at levels central to the photochemical system itself." When observers are suddenly exposed, without their knowledge, to variations in oxygen tension the results vary with the type of respiratory response. Voluntary hyperventilation with room or oxygen-rich air will cause the visual

threshold to fall to approximately half the normal value within five to ten minutes. This change is due primarily to alkalosis induced by the hyperventilation and can be abolished or reversed by adding carbon dioxide to the mixtures. With 5 per cent carbon dioxide the threshold is approximately doubled. "In general these experiments support the thesis that the visual threshold offers a practicable quantitative index of physiological imbalance." The observed changes in threshold are slight compared with the total range of adaptation, being two- to fourfold. This the authors consider a measure of the variation which disturbances central to the photochemical system contribute to the visual threshold.

Critical fusion frequency.—The critical fusion frequency is recognized as one of the most useful and delicate measures of visual sensitivity. Miller has investigated children but found no distinct trend with age between six and eighteen years. A slight sex difference, girls being somewhat lower than boys, is the only positive finding. Bartlett & Hudson (2) contribute a mathematical treatment of the relation of brightness and rate without experimental data. Simonson & Enzer (95) claim that there is a "consistent decrease of fusion frequency of flicker resulting from fatigue of the central nervous system in light or moderate occupational work. There is evidence that the decrease runs parallel to subjective fatigue."

PATTERN VISION

Pattern or form vision and the capacity for accurate image formation which it requires constitute a field which, because of its great practical importance as well as its theoretical interest, is constantly being worked.

Refraction.—The success of the eye as an image forming organ rests on a nice balance between the power of the refractive surfaces and the length of the globe. Glasses measure this discrepancy and its amount may be determined very accurately, an interval of $1/8$ D or its equivalent $1/20$ mm. being measurable with consistency. The elements in this balance are determinable with very unequal accuracy; the corneal refraction may be easily and exactly measured, the lenticular refraction with far greater difficulty and far less accuracy, while the axial length has been a mere inference in the living and a crude approximation *post mortem*. Goldmann & Hagen (35) have determined for the first time most of these elements in the living eye with sufficient accuracy to permit signifi-

cant analyses of certain interrelations. The method of determining the length of the globe, an essential feature, is based upon the earlier work of Rushton (90). If a narrow beam of x-rays strikes the dark adapted eye at right angles to the optic axis, a circle of light corresponding to an optical section of the globe is seen. If the slit is moved posteriorly by an apparatus orientated with respect to the cornea, the circle decreases concentrically about the fixation point and disappears. In this manner the length of the globe can be determined to within about 0.1 mm. In addition Goldmann measured the image and object as follows. An x-ray tube just below the line of sight projected two beams through the eye and since these are not refracted, the separation of the lines, here about 5 mm., could be accurately determined at the retina. This "image," consisting of two short vertical lines, was seen as an "object" on a wall and matched in a series of trials with lines projected from a lantern. From these data—"object" size and distance, "image" size and distance—the total refractive power of the eye was calculated with an accuracy, according to the authors, of about 0.5 D in the better observers. The corneal refraction was also measured and that due to the lens calculated, giving a result probable less accurate since they did not measure the separation of cornea and lens (depth of anterior chamber) but assumed a constant from the schematic eye. By these ingenious methods Goldmann & Hagen (35) measured eighteen eyes, giving the first satisfactorily complete and accurate measurements of the living human eye which have been made. The authors state that the values obtained agree satisfactorily with those of Gullstrand's schematic eye; this is borne out by the following values calculated from the six cases of emmetropia.

	Goldmann	Gullstrand
Total refraction	59.22 D	58.64 D
Cornea refraction	43.07 D	43.05 D
Lens refraction	19.23 D	19.11 D
Length of globe	23.4 mm.	24.00 mm.

The interrelations of these values will be of great interest when more measurements are available. The possible correlations have been plotted and those promising significant coefficients have been calculated from Goldmann's data. There is a negative correlation of .87 between the refractive state and the length of the globe in the sense that the myopic eyes were in general long in

inverse proportion to the degree of myopia; apparently most were cases of axial myopia. This coefficient of correlation is significant, the 95 per cent confidence limits being .96 and .60, but because of the small numbers the other coefficients are not significant. The corneal refraction appears to be positively correlated with the total refractive power and the refractive state and negatively with the length of the globe.

There is some indication that the values are less exact than might have been hoped, perhaps from the approximations used in the methods of calculation; for example, the location of the second principal point calculated from the total refractive power lies too near the cornea. It is to be hoped that the authors will undertake a more extensive series of measurements and present the original data as well as their calculations.

Myopia, a common and troublesome refractive defect, has received the usual amount of attention. The controversy over its origin started by Cohn in 1866 is still active and a score of views and suggestions have been capitalized by "treatments," the money-getting powers of which are beyond dispute. Cowan (14) contributes a sensible article on myopia aimed at the ophthalmologist rather than the physiologist. His views on the origin of myopia, which appear sound, unfortunately lack statistical support. The following quotation is not an overstatement on the side of "causes" and each cause has a "treatment."

Almost every conceivable reason has been offered for the causation of myopia, a refractive error: overaction of the ciliary muscle by excessive close work and accommodation; stretching of the choroid by pulling of the ciliary muscle; deficient effect of the action of the extraocular muscles; increase of the intraocular pressure with weakness of the sclera; cardiovascular disease; pulling on the optic nerves by gravitation; lack of calcium; increase of blood in the orbital tissues and the eye; disproportion of the size of the retina to the eyeball; through the turnstile of astigmatism; bending of the upper part of the body; congestion by manual labor; shape of the orbits; lack of vitamins; glandular dysfunction; measles, whooping cough, and bronchitis; obstruction of lymphatic drainage; prenatal and inherited weakness; and many others, including, of course, tuberculosis, syphilis, and sinus disease. Junius said that light, a physical and chemical stimulus of the retina, may become a malign influence in the predisposed, and Incze associated myopia with flat feet.

Some of these theories have many adherents, some have a few, and many have only one, the proposer. Every theory that has ever been offered can be disproved by argument, clinical experience, or experimental investigation, and mostly this has been done by the author of a hypothesis of his own.

In the absence of any symptoms of disease, myopia, regardless of degree, is a simple error of refraction due merely to the fact that the retina lies behind the posterior principal focal plane of the dioptric system of the eye. There is no known way to prevent, arrest, or cure it.

Brown (6), under the oddly worded title of "Use-Abuse theory of changes in refraction versus biological theory," presents data on refractive changes with age bearing on what Parsons has called "development myopia." According to his figures, based on some 13,000 measurements on 1,737 persons, the hyperopia present in the child under two years increases up to the age of six or seven and then decreases steadily and uniformly to the early thirties when emmetropia is the average condition. Values up to the age of fifty, based on fewer cases, are more irregular and apparently of little significance. What on the average appears as a decrease of hyperopia from seven years into the early twenties will appear in children initially emmetropic as a shift to myopia and in myopes as an increase of myopia. This is the type of data that has given rise to what Brown has called the "biologic" view that the normal growth of the eye includes a period of increasing length or decreasing refractive power which, since it corresponds to school age has been blamed by some on close use of the eyes. It is fortunate that the distribution of refraction with age and other data are not presented. Although the changes in refraction present an orderly picture, there are suggestions that the data are not wholly typical. Clinical data from a large hospital always suffer markedly from selection and 19 per cent of myopia during the first two years is higher than that shown by other data, usually 5 per cent or less.

Whatever the origin and course of refractive errors, it is obviously important to examine children during the school years when the lack of glasses, if they are needed, is both a serious handicap in school work and a possible unfavorable influence on vision in future life. English, Shmukler & Cowan (23) compared three methods. One followed the Pennsylvania State instructions and included use of Snellen types, a second was a routine sponsored by the NEA, including use of Snellen types and a general examination, and the third was a commercial test consisting of a special set of stereoscopic slides (Betts). One hundred and eleven children were given a complete examination by an ophthalmologist. The NEA test proved the most satisfactory since it properly referred for further examination as large a number as any and "passed"

the smallest number of children who were actually in need of treatment. The commercial test, one of those being exploited on a national scale, actually passed children over half of whom were in need of glasses or professional treatment.

It is well known that after cataract operations distortion of the cornea by the asymmetrical scar causes astigmatism. Winkler-Prins, (110) claiming that the distortion is due to the width of the scar, has excluded even a clot from between the edges of the cut by touching the margins with a 3 per cent solution of sodium citrate. Astigmatism is said to be almost wholly prevented.

Aniseikonia has attracted much interest in recent years and many papers have been encountered in the period of this review. Aniseikonia literally means "unequal images" but the term, according to Lancaster, is usually limited to those cases showing abnormal differences in images. It should be pointed out that, as measured, the difference is subjective and is a resultant between the physical differences in the images and the space values of the retina, which are unequal, for example, on the nasal and on the temporal sides.

The classification of aniseikonia proposed by Sheppard appears the most satisfactory (92). The two main classes are inherent or anatomical, in which the structure of the retina is innately or pathologically unlike in the two eyes (as in retinal metamorphosis) and induced, in which a difference in magnification is introduced in correcting anisometropia.

For the detection of the condition ingenious and elaborate eikonometers have been devised and for its correction "size" lenses which alter the size of the images without changing the vergence. It has become a refractive vogue but will in time presumably settle into its proper role as a special refractive technic.

Post (88) in an editorial on "The future of aniseikonia" points out that "any therapy that depends primarily on subjective elements for proof of its efficacy must travel a long and hard road." It is undoubtedly this element which leads to such divergence of opinion and to the "cult" attitude on the part of many of its proponents.

As to its incidence Burian (8) states that in one hundred consecutive clinic patients, thirty-six showed 1 per cent or less; fifty-five, 1 to 2 per cent; and nine, more than 2 per cent. The degree of aniseikonia is stated in terms of percentage difference in size of

the images in the two eyes as measured by the eikonometer. While, of course, the degree of aniseikonia which requires treatment varies with the person, Hicks (48) says that he has not found any person who secured relief from the correction of less than 1 per cent and that 5 per cent is the maximum compatible with binocular vision.

On the other hand Peckham dealing with a selected group found a very low incidence (86). Of 252 naval aviation cadets and instructors required to have vision of 20/20 without correction in each eye, 92 per cent were shown by the eikonometer to have aniseikonia of less than 0.5 per cent, 5 per cent to have 0.5 per cent but less than 0.75 per cent, and 3 per cent to have 0.75 per cent or more. Only one individual (0.4 per cent) showed an aniseikonia greater than 1 per cent—actually 1.25 per cent. It is clear that careful selection for visual acuity excludes nearly all cases of aniseikonia. Tested with the "leaf room" and a plane with and without "size" lenses, 33 per cent showed "a spatial disorientation of moderate amounts, but amounts that might be aniseikonia." The leaf room, according to Ogle (83), is a cube some 7 ft. on a side viewed by the subject from the center of the open side. "To the inside surfaces (painted black) are stapled artificial vines with the leaves individually adjusted so that they stand out uniformly from the surface. . . . The nature of the binocular spatial localization is determined from the subject's description of the apparent positions, shapes and sizes of the walls, ceiling and floor and of the leaves themselves as he looks into the room." Viewing the room with and without various "size lenses" the subject's answers regarding distortions are recorded. How these are scored and interpreted is not stated. "The leaf room is especially valuable in revealing several other types of ocular image 'incongruities' " so that interpretation would seem difficult.

General articles by Birge (5) and Lancaster (62 to 65) are valuable for orientation and should be consulted by those interested.

The subjective nature of the defect is emphasized by the phenomenon of "compensation," the existence of which is established although it is not understood. "Careful aniseikonia corrections will at times give 'horror fusionis.'" Jackson (54) cites two cases of comfortable binocular vision in which there were marked size differences between the two images.

For the physiologist aniseikonia is chiefly of interest because of its effect on binocular vision and its relation to perceived size;

these latter aspects will not be fruitful until much more fundamental research has been carried out.

Accommodation.—Koke (60) injected thorium dioxide into the eyes of cats and, after it had been taken up and distributed by phagocytes, took stereoscopic roentgenograms with the eyes under cycloplegics or cyclotonics. By this method he was able to observe changes in the relations of the ciliary processes, iris, lens, and the divisions of the vitreous. "The outstanding changes," says Koke, "in an eye under the influence of physostigmine, as shown by roentgenograms, are conoid deformation of the posterior surface of the lens, an increase of the axial diameter of the lens and an axialward forward movement of the tertiary vitreous." Unfortunately the reproductions of the x-rays are not clear enough to permit analysis and the composite drawings are not labelled. The increase in the axial diameter of the lens is clear, and it apparently shows a slight peripheral flattening (see Nordenson below on the use of "conoid"); changes are apparent in the vitreous but hard to interpret. Koke gives the following description of the action of these parts in accommodation.

Since these alterations must be due to the ciliary muscle, it is assumed that the main action of the muscle is constriction of the tertiary vitreous. This sphincter-like action rolls the tertiary vitreous inward and upward against the lens and backward against the secondary vitreous. The secondary vitreous tends to expand at the ora serrata but is prevented from doing so by the attenuated posterior extremity of the ciliary muscle. The equatorial diameter of the lens does not decrease, because there are no circular fibers in the ciliary muscle to relax the anterior fibers of the zonule and the connective tissue in the anterior portion of the ciliary body blends with the meshwork fibers and tends to restrict constriction of the anterior zonule.

It is difficult to visualize the mechanism here described. Koke points out that the cat lacks the circular fibers found in the ciliary muscle of man and says, "how the mechanism of accommodation in the cat eye corresponds to that of the eye of man is speculative."

Sachs also studied accommodation in the eye of the cat and of the dog (91). In general his results agree with the classical observations of Hensen & Voelckers; the external (sclera) surface of the ciliary body, as seen through a window cut in the sclera, moves forward about half a millimeter. In addition he has determined the force of this movement, which may exceed 200 mg., and, in a zone 2 to 5 mm. posterior to the limbus, has noted a slight backward movement of the anterior coronal region of the ciliary body. This back-

ward movement is not seen except with contractions of enough vigor to produce a well marked forward movement in most of the ciliary body. He considers that it may result from a certain amount of "give" in the attachment of the radial fibers of the ciliary muscle (the circular fibers are absent in the cat and dog) and that its occurrence does not contradict the usually accepted idea of the ciliary mechanism founded upon Helmholtz's theory.

Nordenson (82) objects to certain points in Fincham's treatment of accommodation. He says that Fincham's description of the anterior surface of the accommodated lens as "conoid" is inexact and, in as far as he is able to interpret it, incorrect. As earlier measured by Nordenson, the curvature of the anterior surface in accommodation increases peripherally as well as centrally; centrally the radius decreased from 9.54 mm. to 7.38 mm. and at approximately 20°, from 16.2 to 10.62 mm. Secondly he thinks that there is insufficient evidence of the modeling of the anterior surface ascribed by Fincham to differences in the thickness of the capsule. He presents measurements of the curvature of an excised human lens in its capsule allowed to swell in distilled water.

The first criticism seems justified; surfaces should be described in geometrical terms supported by measurements, not in vague terms tinged, as here, with the view which the writer is espousing. The cogency of the experiment offered in support of the second point is less clear. In the exaggerated swelling of the lens in distilled water there is at least a possibility that, owing to the fibrous nature of the lens, the increase would not be equal in all directions. In the radii given in the table below, moreover, the same proportion is not maintained at the three points measured, but the radii of the peripheral points have increased less than the central radii.

RADII OF LENS IN DISTILLED WATER

Position	After 4 hrs.	After 48 hrs.	Relative degree of swelling
5°	6.3 mm.	8.1 mm.	100.0
15	7.2	9.0	95.2
25	7.4	9.2	96.6

Visual acuity.—Although visual acuity has long been studied because of its practical importance, its mechanism still eludes the workers of today. Shlaer, Smith & Chase (94) have extended the

earlier work of Shlaer (93) with white light, by testing with two wavelengths chosen to differentiate between contributions of the rods and of the cones to acuity with changing illumination. The red (670 $m\mu$) stimulates the cones only and the blue (490 $m\mu$) stimulates both, although it appears white with the rods and blue with the cones.

The test objects were presented at a distance of one meter in the center of a uniform field about 30° in diameter and were seen through an artificial pupil. Two test objects were used, a grating with equal bars and spaces and a broken circle or C in which the width of the line and of the gap were one-fifth the outside diameter of the circle. These test objects could be varied in size and presented in different positions; the illumination was variable over a range of approximately 9 log units.

In general the results confirm Shlaer's earlier findings, visual acuity increasing with increasing illumination. Plotted as visual acuity on log illumination the course is sigmoid; if log visual acuity is plotted on log illumination a curve convex upward and of constantly decreasing slope results. The curves for the C and the grating are similar in shape but that for the grating does not rise as high (lower maximal acuity) and is displaced about 1 log toward lower illuminations, i.e., at low intensities the C requires about ten times as much light to give the same acuity.

In both curves a discontinuity occurs, more distinct in the log log plot, at a visual acuity of about 0.16, but which, because of the relation stated above, falls at a retinal illumination of about -1.5 log photons for the grating and about -0.5 log photons for the C. This was interpreted by Hecht & Shlaer (45) as the transition between rod and cone vision. The recent work confirms the earlier interpretation; with the blue light the same discontinuity was found but with the red there was no break and the line could be followed through all illuminations as a pure cone function.

Shlaer, Smith & Chase (94) claim that no improvement in acuity occurs above one thousand photons so that here illumination is not the limiting factor. Using the grating and white light a pupil less than 2.35 mm. in diameter was found to limit acuity; with colored light the longer wavelengths were found to require larger pupils. The relation of the pupil size to the C test object is different; neither the increase in diameter of the pupil from 2 to 3 mm. or the use of monochromatic light improves acuity.

They state that "both the pure rod and cone data with the C

test object are precisely described by one form of the stationary state equation. With the grating test object and a nonlimiting pupil, the pure rod and cone data are described by another form of the same equation in which the curve is half as steep." Crozier has applied the probability integral to various visual functions and McFarland & Halperin (77) have extended this application to visual acuity, with good agreement. They also point out that one form of the stationary state equation is identical with the Verhulst logistic curve. Some of the data giving a slightly asymmetrical sigmoid curve would probably be well fitted with a Gompertz curve.

The curves published by Shlaer, Smith & Chase (94) appear satisfactorily fitted to the data and are useful as descriptions of the relationships between illumination and acuity. A protest should, however, be entered against the logic by which even a "precise" fit is taken to prove the nature of a process. In the present case of visual acuity, two types of formulae have been used and one or two others would probably give fits which, to casual inspection, would be satisfactory. If one formula is to be preferred to another the statistical reliability (based, for example, on the sum of the squared residuals) must be shown to be greater in that case. In biological data it is common that the variability prevents a decision and two or more formulae may give about equally "good" fits. Even if a particular fit is shown to be statistically superior to one or several other mathematical forms, this does not, and in the nature of things cannot, prove that the mechanism in question is identical with some process for which the formula is commonly used. This point is clearly stated by R. A. Fisher, the English statistician:

It will be seen that the test of significance does no more, and attempts no more, than to answer the straightforward question, "Could these samples have been drawn from the same population?" It calculates a probability. If the probability is very small the answer is "No." If it is not so small as to reach the level of significance required, the answer is "Yes, they could." The answer is never, "Yes, they must have been."

The correlation observed between acuity and illumination, for example, may be of a form which does not preclude a particular chemical reaction, but proof that this reaction is "causally" involved, requires chemical proof independent of the statistical data.

Visual acuity is also considered in papers by Berger (3), and Berger, McFarland, Halperin & Niven (4). In both papers an increase in the minimum resolvable angle with an increase in illumin-

ation is reported. This is in contrast to the results reported above for Shlaer, Smith & Chase (94) and a long line of investigators extending back to König in 1897, who have found an increase of acuity with increase in illumination.

This contradiction, as well as the lesser one found by Shlaer, Smith & Chase (94) between the grating and the C, emphasizes that visual acuity must be defined operationally and that results given without stating the nature of the test object, the illumination of test object, and ground and other elements of the stimulus pattern have no significance.

Berger in both studies (3, 4) used as a test object two luminous points (circular with a visual angle of 26.1") the separation of which could be varied and to this situation Berger restricts the term "resolving power." Berger in the earlier paper (3) also used a broken circle but of a different design from Landolt's C used by Shaler, Smith & Chase (94). Berger's C was luminous on a dark ground (the reverse of Landolt's) and at the distance used (7.9 m.) had an outer diameter of 16.5', an inner diameter of 13.1', the line was 2.7' wide and the gap alone was variable with values up to about 2'.

The spread of the light in the images of the luminous points (irradiation) is very marked as may be seen from the sketches made by Berger's subjects. In consequence the points have to be more widely separated at higher illuminations in order that they may be seen as separate.

Berger, McFarland, Halperin & Niven (4) found a decrease in resolving power with low oxygen tensions as has been shown for the visual threshold. They state that the decrease in acuity with low oxygen and other "effects of anoxia are attributable not to any changes in the photochemical reactions which take place in the retina, but rather to other alterations in the *neural* elements of the retina, the brain, or the connections between them." In support they cite among other reasons the findings of Chase & Hagen (10) that *in vitro* the decomposition of visual purple is not affected by the presence or absence of oxygen. When completely dark adapted, with full opportunity for regeneration of the visual purple, low oxygen reduces the sensitivity.

Unfortunately Berger and his associates have not yet attempted to analyze the mechanism of image change with illumination, an important phase of the problem of acuity.

Carson (9) has devised an instrument for exposing ordinary

Snellen letters for varying lengths of time. Officers and aviation pilots at their annual examination were tested on the machine in the following manner. Visual acuity was determined with a Snellen chart and letters of the same size were exposed in the machine and the exposure time progressively reduced until the subject failed to recognize the letters. Although there were some persons who proved abnormally slow in recognition, in general those with the higher acuity proved to have the shorter recognition time. These findings agree with the earlier work, for instance, of Kellogg (57) and of Fernberger (25), which showed that the reaction time was shorter when the task was easier.

Articles by Hartridge (43) and by Crisp (15) dealing with Aldous Huxley's *The art of seeing* deserve mention in connection with visual acuity. Huxley has suffered since childhood from corneal opacities and refractive defects which have made reading an ordeal. In his book Huxley (51) sharply attacks the medical profession for their incompetence in dealing with such visual defects as his, inveighs against glasses, "eyes fitted with these tend to grow progressively weaker and to require stronger glasses for their correction," and upbraids doctors for regarding as "unorthodox the methods of visual reeducation such as those of Bates" by which Huxley's "eyes might well have been cured in a few months."

Corneal opacities improve slowly and finally become stationary but vision fluctuates with the size of the pupil in what often seems to the uninitiated a capricious manner. Sufferers from such fluctuating defects offer fertile soil for cults such as those bearing the name of the late Bates; Huxley is no exception and expounds many of the Bates procedures in what Crisp calls "a fine frenzy of psychologic discourse" (15). It is fortunate that Huxley's enthusiasm should find no better object than to rouse false hopes in sufferers from those types of poor vision for whom little can be done and to increase the profits of visual cultists.

The procedures of Huxley insofar as they have any merit are simple acts of relaxation—such as "palming"—invested with so impressive a ritual that no devotee feels that he is wasting time or forgets to carry them out. Any one who realizes that lenses cannot perform miracles and is a bit impressed by the argument that glasses are "crutches" would do well to compare the practice of today regarding glasses with that of one hundred years ago as vividly pictured by Lancaster (65). Before Donders had laid the basis of modern refraction in 1864 the young English hyperope

was cut off from any life requiring exacting use of the eyes and condemned to the sheep ranches of Australia or the woods of Canada.

COLOR VISION

The increase of color testing incident to the war and the preparation of routine and often inadequate summaries for special groups or occasions have swollen the number of papers on color vision. There are, however, a few scholarly and valuable papers such as those of Murray (80, 81) and of Judd (56).

In the field of color vision tests the old struggle between ease and accuracy is now raging. The harassed examiner wants a short, dogmatic, sure-fire test; careful examination of color vision requires both a skilled operator and complex apparatus such as a spectrophotometer and the results often require interpretation.

The supply of two of the most used tests, the Stilling and the Ishihara, was cut off by the war and a domestic edition of pseudoisochromatic plates based on the Ishihara test was issued by the American Optical Company, but the chromas of the ink are not easy to match and the performance on such a new edition must be reevaluated. New tests have been hastily devised or old ones revived to fill the gaps despite the fact that Haupt, writing on color tests, listed 335 titles up to 1928 (44). As a result of this confusion, "color blindness" is merely failure to pass a particular test or a particular scoring of a particular test, and has largely lost its meaning.

A critical evaluation of the American edition of the pseudoisochromatic plates has been made by Gallagher, Gallagher & Sloane (32, 33). In testing 726 boys according to the publishers directions they found a large number of errors among boys believed normal. This led to a reexamination of 132 normal boys, 104 normal girls, 30 color deficient boys, 3 color deficient girls, and 5 "doubtful" boys. Of the forty plates used some proved more critical than others, for example, one plate was not missed by any of the 274 children, either normal or color deficient. Other plates were missed by one-fifth to one-half of the normal boys and girls. Tables are given of the numbers and types of mistakes. On the basis of the study, 29 plates were selected as a shortened and more critical test. None of the normal children failed more than one of the 29 plates, and no single plate was failed by less than 16 per cent of the color deficient group. The paper should be studied by all who have occasion to use the test. It should be emphasized that the study is

a purely empirical one and does not even mention color theories.

One of the revisions is that of the Nela test, first developed by Knight Dunlap in the Nela Laboratories in 1923, but recently studied and revised by Loken (69), a student of Dunlap. The test consists of a series of skeins of colored yarn arranged in triplets; the subject is asked which of the two outer skeins most closely resembles the center one in hue. It originally consisted of 22 items, later it was expanded to 47 triplets by Haupt (44), a student of Dunlap. Loken has reduced it to 24 items. In its revised form it was administered to 979 students and their answers analyzed. These data are chiefly the total error scores and the distribution of errors by triplet numbers.

Lokey (69) finds that males and females show no significant difference ($P=0.15$) on the Nela test and on the Ishihara test the difference merely approaches significance ($P=.06$). This is surprising in view of the differences usually found between men and women in samples of this size. In the discussion he suggests that "the line drawn between color blindness and its absence has been arbitrary," and that the "color-weak" group is the more important to detect. Speaking of the Ishihara test he says, "The usual practice . . . is to allow one error, including all those making more than one error, in the 'color-blind' group . . . according to this criterion 14.2 per cent of the men and 9.7 per cent of the women are to be classed as 'color-blind.'" These are surprising results, difficult to reconcile with the great body of similar work.

Lokey (69) points out that a comparison of the Nela and the Ishihara tests "reveals discrepancies in error scores which can probably be explained in terms of intensity and acuity factors operating in the Ishihara test." He considers the Nela test superior.

Data on reliability were obtained by a retest, for part of the subjects immediately, for some, a week later. A very pronounced practice effect is evident, as pointed out by Lokey although he does not calculate the change. Comparison shows that for the men the total errors on the retest were 37 per cent of the test errors and in the case of women 48 per cent. Reliability coefficients calculated on the test retest data vary from 0.37 to 0.87 on various items with an average for the entire test of 0.64. The reproducibility of the test seems hardly satisfactory.

Perhaps the most interesting and controversial feature of the report is the use of vitamin A as a "remedial agent." One of the

men who had made a high error score on all tests offered to serve as subject; after 25,000 units of vitamin A daily for twenty-five days he was retested and made far fewer errors. On the Nela test his total error score was 18, on the retest 6, or 33 per cent; it will be recalled that for the entire group of men the retest error score was 37 per cent of the test score.

Loken later selected sixteen color-weak men, divided them into "matched" groups of eight each and gave each man a capsule per day for twelve days. The capsules for the "dosage" group contained 25,000 units of vitamin A, for the control group, milk-sugar. The total error score of the "dosage" group was reduced to 43 per cent, an improvement rather less than the average. Because of this fact, the lesser improvement of the control group which appears significantly different is not impressive.

In an abstract Dunlap & Loken (20) cite the above data and in addition the fact that thirty persons reached by mail had been advised to take vitamin A and that twenty had written and reported "significant improvement."

These results have been sharply criticized. Elder (22) failed to obtain similar results. In a group of sixteen college men with defective color vision only two with minor deficiencies showed improvement. Later, speaking of a group of forty-one who finished an eight week treatment (total vitamin A, 1,400,000 units) the author says, "no significant improvement in color sensitivity was shown by any individual."

Murray in a paper criticizing Loken's report (80) says, "Finally, the Loken-Dunlap broadcasting of 'cures' of color blindness through dosage, however innocent in intent, appears to the writer to be as unethical as a premature announcement of a cancer or tuberculosis 'cure'—rousing false hopes and promoting the use of charlatanry." Among the "cures" might be mentioned that of Lepper (67) an optometrist who has done an extensive business in treating men who had failed to pass the routine color examinations of the army and navy. When investigated by the American Medical Association he produced proof that many men once failed had been enabled to pass the tests and had been accepted into the armed forces. His treatment consisted of flooding the eye with light through a filter of a color appropriate to the defect and extensive coaching by a person of normal color vision under whose directions the subject traced the patterns of the pseudoisochromatic plates. The American Medical Association suggested that Lep-

per and his disciples "might limit their promotion of the method to the statement that they teach men to pass the tests for color vision and avoid carefully the use of the word 'cure' in any relation to color blindness."

It is clear that the color vision tests at present in use are not satisfactory and that along with them our classification and nomenclature of types should be revised perhaps with the abandonment of the term "color blindness." Some activity in this quarter is in progress but it is too early to assess its promise.

Two articles on types of color vision may be mentioned. Lewis & Mandelbaum (68) describe three additional cases of achromatopsia or complete color blindness (not monochromatic total color blindness). While these three showed low acuity, central scotomata and visibility curves with a maximum of 510 $m\mu$, thus agreeing with the suggestion of nonfunctioning cones, they are "atypical" in that the adaptation curves show clearly the early photopic step ascribed to the cones.

Gray (42) proposes a modification of the classification of color defects and their inheritance that agrees more closely with their incidence in the general population. Both of these papers indicate the complexity of the subject and support the protest against the hard and fast categories of the usual classification.

It is necessary to omit consideration of a large number of papers dealing with the technical aspects of color specification on a trichromatic basis, the fundamental relations to spectrophotometry, the geometrical relations on the color surface of discriminable differences, the modifications introduced by adaptation, the visibility or lamprosity functions, the relation of the color surface to color systems, such as the Munsell, color nomenclature, and the like. Their highly technical nature and the necessity of presenting the current changes against an adequate background make it difficult to compress the advances into a limited space; those interested will find in the bibliographies of a few selected papers an introduction to this important and active field (56, 80, 81).

SPACE PERCEPTION

Retinal orientation.—A study of a fundamental aspect of retinal orientation in the newt (*Triturus viridescens*) has been reported by Sperry (96). The eye muscles were cut and the eye rotated through 180° (using the horizontal stripe of the iris as an index) and retained in this position. In snapping at food the operated animals

showed a disorientation, conforming to the abnormal retinal position, which was not corrected by four and one-half months' experience and which rendered them less well adapted than blind individuals. "The results demonstrate an unadaptable rigidity of central coordination mechanisms in the visumotor system of urodeles comparable to the implasticity of spinal organization found in amphibians and rats." Many features of the motility of the eye, for example the reflex rotation about the optic axis, indicate that space values, such as shown in Sperry's experiment, are basic to orientation and space perception.

Eye dominance.—Wile (109) has studied the handedness and eyedness of fifty children presenting behavior problems. The large number of left eyed children and children right handed by conversion is notable, each group including about three-fifths of the total as well as the small number of native right handed, but the numbers are too small for analysis. The paper is therefore suggestive to those interested in behavior rather than in the eye. Lebensohn (66) finds that right eyed men show slightly better marksmanship, but this is influenced by mechanical features of the operation of the gun and therefore not easy of analysis. He gives data on a "sample" of recruits in which, although less common, left handedness and left eyedness appear independent; this agrees with the results of earlier workers. It is doubtful, however, that the sample is random. In a second group of 856 right handed men, 16 per cent are reported as left eyed, a proportion much smaller than found in the first group and probably more nearly correct.

Accommodation and convergence.—A recomparison of the relative contribution of accommodation and convergence to the judgment of distance has been made by Grant (41). He used, instead of the plain milk glass disks of earlier workers, a target carrying letters to insure a definite stimulus to accommodation. Whereas Swenson, an earlier worker in this field, had found convergence far more effective than accommodation, Grant found them about equally important. There was a recognized but unexplained tendency markedly to overestimate the near and to underestimate the distant positions which may represent the effect of some important but unrecognized cue of distance.

Binocular space perception.—It is indicative of the excellence of the contributions of Ewald Hering (47) to the physiology of the eye that a section on "Raumsinn und die Bewegungen des Auges" written in 1879 for Hermann's *Handbuch der Physiologie* should

have been translated into English during the past year. Franklin (27) discusses certain of the broader aspects of binocular vision from a wholesomely dynamic viewpoint. "The basic theme of our presentation," he says, "is that *stereopsis, fusion and projection are not purely sensory, or sensory-psychic abstractions*—as classical theory would have it—but are *eye-limb-body, locomotion, and prehension functions or processes*—ancient spatial-reaction complexes, in which the *body and limb movements have evolved from an actual to a potential form.*" His views, which show the influence of Chevasse, are clothed in a rather intricate and forbidding terminology but they are suggestive and will repay study.

Werner presents a dynamic field theory of binocular depth perception (108) which must be considered in the light of earlier papers (106, 107). Working with simple stereoscopic diagrams, often consisting of only three lines, he has shown how the "width" and "depth" values of a line seen by one eye are influenced by the position of a line seen by the other eye. An hypothesis of depth perception, difficult to present briefly, is reached. "Binocular stereopsis is connected with functional change of projection. Direction of depth and direction of displacement are strictly correlated. Functional displacement nasally signifies a position in front of, and displacement toward the temporal side a position behind the fixation plane." Despite the fact that such a field theory ignores the question of physiological mechanisms and their loci, assuming like thermodynamics an overall view, it offers more opportunity for effective experimental work and promises a more fundamental understanding of a difficult problem than other recent works.

General papers include those by Lancaster, a chatty and shrewd "Fifty years' experience in ocular motility," (62) and an article on the terminology of binocular vision (64), a preliminary report of a committee attempting to standardize the far from uniform usage in the field.

Eye muscle training.—Fowler (26) gives a discouraging picture. "Pure orthoptic training exercises . . . undertaken and carried out in 182 cases of strabismus . . . under thoroughly favorable conditions . . . were a failure in 180 cases. . . . Two patients . . . were benefited."

Burri (7) feels that the binocular mechanism develops during childhood and does not rest on an inherent "fusion faculty." "To obtain the truest picture of how fusion is learned one should . . .

study a person who had never had any practice in binocular vision, [but] these . . . would be difficult to secure. It seems possible to throw some light on the problem from . . . the training in binocular vision of people with . . . strabismus." The monthly progress of five out of six persons studied gives what she considers typical learning curves; one failed to improve. The values plotted are the deviations of the eyes from parallelism; if these may be looked upon as errors in the functioning of the binocular mechanism, she is justified in her interpretation.

Binocular tests.—Two new tests of binocular vision have appeared and it is possible that others have been developed which will not be released until after the war. Verhoeff (102) uses a piece of thick plate glass with paper strips glued to either side and Davidson white headed pins projecting different distances from a card for office testing. Redway (89) has considered the requirements for stereopsis in various phases of industry. Davidson (17) likewise has surveyed industrial requirements. He reports a binocular threshold of 20" in 64 per cent of "normal" persons and gives this classification: 20", normal; 29" to 46", fair; 46" to 120", poor; over 120", without demonstrable binocular stereopsis.

Measurement of phorias.—Deviations from the normal relations of the optic axes are measured by phorometers, all of which operate on the same principle, that of removing the impulse to fusion and then measuring the relative positions of the eyes. Testing is commonly done at six meters and at the reading distance. Among the gadgets which confuse and mislead the testers are the widely exploited sublimized stereoscopes. If a vertical arrow is presented to one eye and a horizontal row of numbered dots to the other, one aim of the phorometer is fulfilled, that of avoiding the impulse to fusion, and the dot to which the arrow points will indicate the relative position of the eyes. The interpretation is not as easy. If the instrument is optically correct, that is, if the slide is at the principal focus of the paired viewing lenses and the lenses are separated the same distance as the eyes, the situation will be mechanically equivalent to testing at six meters, but all persons are more or less influenced by the knowledge that they are looking at a near object and react with differing degrees of convergence. If now the tester can guess the particular individual's extra convergence and correct for it and the other shortcomings of his instrument he will arrive at an estimate of the amount of the phoria. A recent com-

parison by Wirt (111) of two types of stereoscope and a more conventional phorometer (unfortunately not the best) clearly shows the greater variability of the stereoscopic tests and the larger reading on a scale with an undisclosed zero. It is cheaper and approximately as accurate to guess in the first place.

Amblyopia.—One of the sequelae of strabismus is the condition known as amblyopia in which the visual acuity is low although the eye appears objectively normal. Feldman & Taylor (24), defining amblyopia by a visual acuity of less than 6/15, found among 68 amblyopes a somewhat greater variability than in normals. Dowl- ing (19) trained a group of thirty-four children showing amblyopia by occlusion of the better eye over periods of from one month to two years. There was a general improvement so that all children attained an acuity of 20/40 and some of 20/20, although the data do not permit an accurate analysis.

CERTAIN GENERAL IMPRESSIONS

Work on vision during the past year has reflected the war conditions in a variety of ways. The output of fundamental work has been reduced, particularly in Europe, and has reached us late or not at all. Visual research directly connected with the war has produced among the English speaking peoples a considerable body of valuable results which will not be released until the close of the war, although abstracts are now in circulation among those engaged in government research. In the Soviet Union there has been much research in spite of the enormous demands on men and resources made by a global war, but the barrier of language, the poor representation of Russian periodicals in the United States, and probably the impounding of findings of possible military importance have reduced its representation with us for the most part to meagre summaries and sometimes to mere titles.

On the other hand the war has released an unfortunately large body of indifferent or poor work. Certain phases of vision have been thrown into relief, such as the testing of visual acuity, adaptation, color vision, and binocular stereopsis, and both the tester and the tested have provoked articles. For the testers there have been summaries of adaptation or color vision, usually drawn from not too recent textbooks by men with little background for selection even in this restricted field. For those testees who failed, and rejections for vision have at times reached one third, there has been

a plague of methods of "curing" their defects, usually in the form of training to pass a specific test—at a price. This situation has been reflected in the more sober and established periodicals by an occasional note of protest. Closely related to this activity is the flowering of commercial gadgetry for testing or training not alone rejected applicants to the armed forces but even more the children in the schools and the workers in industry. The gadgetal salesmanship has been aimed at ophthalmologists and optometrists, at school boards and personnel managers in steel mills and hosiery factories. The appeal, which has been very successful, is to lack of time and to lack of special knowledge. Here is an instrument, finely built and impressive, for the operation of which knowledge is unnecessary and which will test ten men an hour. Our salesman will show the receptionist or the school nurse how to run it in twenty minutes and you can pay for it on the installment plan. These methods of testing tend to place gadgets above fundamental training, to foster an arbitrary one, two, three classification of complex conditions such as color vision and to apply to individuals testing methods which give correct averages for masses of school children or machinists by balancing the mistakes of excess against the mistakes of deficit but which fail correctly to classify the individual in a dangerously large percentage of the cases however they may be used but especially when patterned after the assembly line. Instances have been mentioned on the previous pages. The vision of our children in the schools deserves more care, not by gadgets, but by trained men and women.

It would be unjust to imply that no significant work had appeared during the period. The ingenious methods of Goldmann & Hagen (35) for the measurement of the optical values of the living eye have made available a source of data unknown either to Helmholtz or to Gullstrand in the construction of their schematic eyes. Cogan & Kinsey appear to have found a simple underlying principle in the old problem of corneal transparency. Wagman's measurements of pupillary diameter will undoubtedly replace the values of Reeves which have long been standard. Other outstanding contributions have been noted in the preceding pages. In spite of occasional fads and excesses, a nice balance of basic and applied work is evident in the history of vision and today there is no evidence of any slackening of its healthy growth.

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METABOLIC FUNCTIONS OF THE ENDOCRINE SYSTEM

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Most of the articles mentioned in this review were published between May 1942 and July 1943. Even though the bulk of the scientific literature published during this period was much below that of a prewar year it has not been possible to give anything like a comprehensive survey within the space available. Topics that appear to be of some general interest have therefore been selected for discussion. The greater availability of periodicals from Germany and similar countries has made possible the inclusion of some publications from these sources, and it has been thought worth while to mention one subject that has aroused the greatest interest among German investigators—Bomskov's researches on the functions of the thymus.

Among general review articles which have been published during the year may be mentioned the appearance, in book form (400), of the series of reviews which appeared in the *Journal of the American Medical Association*, largely during 1941, under the general title "Glandular Physiology and Therapy." The proceedings of the *Cold Spring Harbor Symposium* devoted to the relation of hormones to development have also been published (393). Other reviews include those dealing with the hormones of the adrenal cortex and their function (130 to 134, 192), adrenal cortical hypertrophy (135), control of metabolism by the anterior pituitary gland (210 to 213, 235), Simmonds' disease (286), the hormones of the posterior lobe of the pituitary gland (317), the influence of sex hormones on metabolism (350), hormones and diabetes mellitus (235, 398, 399), and the relationship of the thymus to myasthenia gravis (91, 93, 94, 95).

THYROID GLAND

Artificial iodoproteins.—The isolation of crystalline thyroxine from iodinated proteins by Ludwig & Mutzenbecher (1) in 1939, which received confirmation by Harington & Pitt Rivers (2) in the same year, provided the starting point for a series of recent publi-

cations on the means of production of artificial material with thyroid activity (3 to 7) and on the ability of such preparations to stimulate growth in thyroidectomized goats (8) and cattle (9), and in normal mice (10). The long-known action of thyroid preparations in improving the milk and butter fat yield of normal cows can be duplicated with the artificial thyroid-active material (11), and it is to be expected that iodinated proteins will be used to an increasing extent in the future, particularly in agricultural practice.

Radioactive iodine.—Artificially produced radioactive iodine has continued to provide a useful tool for investigations on thyroid physiology, both in the intact animal (12 to 15), and with respect to the *in vitro* formation of thyroxine and diiodotyrosine by thyroid tissue (16, 17, 18). It has provided a means for correlating histological changes with the beginning of thyroid function in the tadpole (19) and in the foetal rat (20). In the latter iodine storage begins at 18 to 19 days at the same time as the formation of glandular acini. Reinhardt (21) has been able to use radio-iodine for determining the completeness of experimental thyroidectomy despite the fact that he and co-workers (22) demonstrated the rapid formation of thyroxine in the liver and other organs when radio-iodine was given to completely thyroidectomized rats.

Radio-iodine has permitted the differential diagnosis of what is termed the exophthalmic type of Graves' disease from the classic form; in the former more iodine was excreted and less retained in the thyroid gland than in the latter condition (23, 23a). The demonstration that radio-iodine may be stored in metastases from thyroid carcinoma (24) opens up interesting possibilities. The therapeutic use of radio-iodine is already under investigation (25, 26).

Thyroid gland and growth.—The diminished growth rate of thyroidectomized rats (27) and of hereditary dwarf mice (28) is increased by thyroid therapy. Thyroid treatment also accelerates growth in normal mice (10, 29, 30). The stimulating influence of thyroid treatment on anabolic processes is well illustrated by the fact that in normal mice thyroxine can increase the growth rate and food intake in such a way that more nitrogen is stored in the tissues of the treated animals for each unit of food taken in than in control mice (29, 30). The growth stimulating influence of thyroid therapy in juvenile myxedema is well known (31), and

Johnston (32, 33) has discussed the possibility that small doses of thyroid administered to growing normal children exert an essentially anabolic stimulus. It is therefore of interest to learn that a proportion of thyrotoxic children are of over average height (34).

The metabolism of calcium and phosphorus in both thyrotoxicosis and myxedema has been investigated in some detail by Robertson (35, 36, 37) who concludes that thyroxine probably directly affects the renal threshold for calcium, the threshold value being raised in myxedema and lowered by the excessive thyroid secretion in thyrotoxicosis. The increase in phosphorus elimination in thyrotoxicosis, and the diminution in myxedema, are probably secondary to the changes in calcium excretion.

Goitrogenic substances.—The development of thyroid hyperplasia in rats receiving a diet containing *Brassica* seed is not prevented by the simultaneous administration of large amounts (100 μ g. per day) of iodine (38), the goitre so produced thus differing from those evoked by a number of other nutritive factors. The pituitary glands of the treated animals show remarkable changes (39), including a rapid increase in the number of basophil cells and a loss of acidophils. These results are consonant with the hypothesis that the goitrogenic agent in *Brassica* seeds does not act directly on the thyroid gland, but stimulates the anterior pituitary lobe to excessive secretion of thyrotropic hormone, an idea that receives support from the finding that the thyroid hyperplasia induced by *Brassica* regresses after hypophysectomy (40). The oral administration of small amounts of allyl thiourea to rats caused not only a thyroid enlargement histologically similar to that induced by *Brassica* diet, but also similar changes in the pituitary glands (41). Richter & Clisby (42) suggest that the hypertrophy of the thyroid gland which they found to follow the oral administration of phenylthiocarbamide to rats might be a reactionary compensation to a reduction of metabolic rate produced by the drug. It is to be expected that such a compensatory hypertrophy would require the cooperative presence of the anterior pituitary lobe. The observation that sulfaguanidine produces a gross enlargement of the thyroid gland in rats (43) was of obvious importance, particularly as the thyroid hypertrophy was accompanied by a marked drop in metabolic rate, and was not prevented or cured by increasing the iodine content of the diet, although the administration of thyroxine was effective (44). MacKenzie & MacKenzie (45) have now fol-

lowed up these earlier observations by investigating the goitrogenic action of a number of sulfonamides and thioureas in rats, mice, and dogs. The reaction was found not to occur in the chick or the guinea pig. As the result of experiments with hypophysectomized and with normal animals the authors conclude that the thyroid-enlarging effect of the sulfonamides and thioureas is probably mediated by the pituitary gland, but Astwood *et al.* (46), as the result of investigations on a similar series of compounds, believe that the thyroid hyperplasia is compensatory to a failure of thyroid hormone synthesis. These workers discuss the possibility that the goitrogenic activity of these drugs resides in their ability to interfere in the process of synthesis of the thyroid hormone. While no final conclusion concerning their mode of action can be drawn it is clear that further work with substances which are capable of producing iodine-refractory goitres may throw much light on the allied problems of thyroid physiology and pathology. In the meantime clinical observations (e.g. 47) continue to provide data which must be considered in relation to the experimental results before a comprehensive conclusion can be made (See p. 577).

Natural antithyroid substances.—Carter and his co-workers (48) conclude that the basal metabolic rate in the rat is normally controlled not by the concentration of the thyroid secretion in the internal medium alone, but by interaction between this secretion and in anti-thyroid substance which they have identified as paraxanthine (1,7-dimethylxanthine). When a normal rat is given small doses of paraxanthine daily by mouth there is a fall of basal metabolic rate which becomes greater with increasing dose until an optimum dose is reached. For a 200 to 250 gm. rat the optimum is 20 to 25 μ g. per day and the basal metabolic rate thus induced is 75 per cent of the normal. If the dose is increased above this optimum value the basal metabolic rate rises again, until it reaches the normal value with double the optimum dose. Parallel results are obtained with the frog heart as a test object. Excess thyroxine can be neutralized by appropriate doses of paraxanthine, and vice versa. The authors have demonstrated the widespread biological occurrence of paraxanthine, and their results open up possibilities that have hitherto played little part in the consideration of hormonal processes.

Reforzo-Membrives (49) has shown that although the pituitary glands of normal rats exert the expected thyrotropic action when

injected into guinea pigs, i.e., they increase the gross weight of the thyroid gland and the height of its epithelium, and raise the basal metabolic rate of the recipient animals, the pituitary glands from rats which have been given desiccated thyroid gland by mouth induce the opposite effects in recipient guinea pigs, i.e., the weight of the thyroid gland and the height of its epithelium are both diminished by about 30 per cent, while the basal metabolic rate of the animal is lowered to 30 to 35 per cent of the normal. The hypophyses of rats fed thyroid gland apparently contain a thyroid-inhibiting substance which causes a decrease in the basal metabolic rate, and many interesting possibilities arise for future consideration. Is it possible that iodine administration—long used in the treatment of Graves' disease—also stimulates the generation in the pituitary gland of a thyroid-inhibiting substance? The position of anti-hormones may also have to be reviewed in the light of these experiments, although it seems improbable that the action of antibodies to thyroglobulin, the administration of which was found by Lerman (50) to induce, in rabbits, myxedema and refractoriness to subsequent treatment with thyroglobulin, is entirely explicable on such a basis.

THE PARATHYROID GLANDS

Site of action of the parathyroid hormone.—Neufeld & Collip (51) stated that parathyroid extracts exert no effect on the serum calcium in rats, cats, or dogs, immediately after nephrectomy, or ligation of the renal vessels or of the ureters. They therefore favored the theory that the parathyroid hormone acts primarily on the excretion of phosphate by the kidney, which it facilitates, and not directly upon bone. But Selye (52) finds that complete nephrectomy in the rat does not prevent the action of parathyroid extract on bone, and concludes that the action of the hormone on bone cannot be mediated by the kidneys. Other workers have reported their failure to demonstrate any effect of parathyroidectomy or of parathyroid injections on the excretion of phosphate or on creatinine clearance in dogs (53), and the balance of evidence still appears to support the theory that parathyroid hormone exerts some direct action on bone.

Control of parathyroid secretion.—No satisfactory evidence has yet been provided that the parathyroid glands are under the close control of anterior pituitary secretions in a manner similar to that

of most of the other endocrine organs. Hypophysectomy results in only a very slight influence in parathyroid histology in the monkey (54) while parathyroid function in the hypophysectomized rat is unimpaired (55), the blood calcium and inorganic phosphorus levels being well maintained even with a low calcium diet. On the other hand, Gergely (56) claims that some abnormalities in calcium metabolism are evident in the hypophysectomized dog, the fasting blood and urine calcium contents being low, with less retention of injected calcium salts. There is evidence that a diminution in blood calcium level directly stimulates the secretory activity of the parathyroid glands (57, 58). Such an effect is demonstrable on a perfused preparation and is presumably a direct humoral control of the glandular activity. A high calcium, low phosphorus diet reduces parathyroid volume in rats (59), the size of the gland being increased by the addition of inorganic phosphorus to the food. Likewise foetal rat parathyroids are depressed by high maternal calcium levels, and stimulated by high serum phosphorus or low calcium levels in the mother (60).

Foster (61) has made a study of the cytology of the normal mouse parathyroid gland in relation to its secretory activity, the transition from the juvenile to the adult state of the gland being described in detail. There appears to be a sharp peak in the curve for mitotic activity during the third week after birth in this species.

THE THYMUS

As in many previous instances experimental work on the function of the thymus appears again to have raised interesting but false hopes, though clinical observations have suggested a new line of approach to the problem which may be of great importance.

The thymus as mediator of hypophyseal influence on metabolism.—Bomskov and his collaborators claim (62 to 77) that the growth-promoting, diabetogenic, and "thymotropic" factors of the anterior hypophysis are identical (65, 66) and exert an action on metabolism which is mediated by the secretion from the thymus of a fat soluble "thymus hormone." According to Bomskov (62 *et seq.*) diabetogenic anterior pituitary extract lowers the liver glycogen content in normal rats but fails to do so if the thymus tissue has first been destroyed by x-irradiation. Although the thymus hormone is (somewhat irregularly) diabetogenic (70, 71)

it exerts no influence on the basal metabolic rate of normal animals (72), the mobilization of the sugar being directed towards increased tissue deposition and growth. Lymphocytosis and leucocytosis regularly follow the administration of thymus hormone to rats (67) and Bomskov concludes from this and other evidence that the hormone is transferred to leucocytes in the thymus and thus transported to the site of action in the body. Although Bomskov's ingenious ideas have attracted some support among his German colleagues (78, 79), most of those who have investigated the problem both in Germany (80 to 84) and in America (85, 86) have been quite unable to confirm his experimental findings. Although Bomskov has discussed and contradicted some of these opposing results (87, 88) his interesting ideas cannot at present be accepted as authenticated by any substantial evidence. As Hoster (86) has pointed out, destructive irradiation of the thymus in rats is not a specific process, and damage to the nearby thyroid, and possibly to the hypophysis, may account for some of Bomskov's results with thymectomized animals. It is pertinent to recall that quite recently Evans and his co-workers (89) have shown in a convincing manner that pituitary growth hormone exerts an unimpaired action in thymectomized rats.

The thymus in relation to myasthenia gravis.—Although it was as long ago as 1901 that a thymic tumor was observed in a patient who had died of myasthenia gravis, and it was in 1913 that the removal of such a tumor was first reported to be followed by improvement in the myasthenic symptoms, yet it is only comparatively recently that sufficient evidence has accumulated to show that in a definite proportion of cases of myasthenic gravis a thymic tumor is found, removal of which may bring about at least a partial remission of the condition. As might be expected, the results of operative treatment published during the past year (11, 90, 91, 92) have been variable, but it is clear that in many instances a striking improvement has followed thymectomy. Harvey and his colleagues (90) were able to demonstrate an increase in the amount of transmitter substance available at the neuromuscular junction, after thymectomy for myasthenia gravis, and although attempts to demonstrate the presence in thymic tissue of a curare-like or myasthenia-producing substance have so far failed (91, 92), McEachern (93) has emphasized the view that the general character of myasthenia gravis suggests an endocrine dis-

order, in which the thymus may well be involved. The present position has recently been reviewed in articles (91, 93, 94, 95) in which good bibliographies will be found. It may be mentioned that Bomskov (96), whose investigations on the function of the thymus have been reviewed above, does not agree with the idea that the thymus is implicated in myasthenia gravis.

PANCREATIC ISLETS

Prolonging the action of insulin by injection of slowly-absorbed compounds of insulin.—Scott & Fisher (97) have reported the preparation of compounds of insulin with a number of bases, while Barnard (98) has described the preparation of insulin ferrihaemochromogen, although no clinical trials of these materials have been reported. On the other hand it is claimed that hexamine-insulin, with an action lasting twelve hours, is of value clinically (99).

The general availability of globin insulin has led to a number of recent clinical investigations (100 to 103) from which some have concluded that this material possesses no striking advantage over the older preparation of protamine zinc insulin (100, 102, 103).

Implantation of tablets of solid material to prolong the action of insulin.—When, in 1937, Deanesly & Parkes introduced the technique of prolonging the action of steroid hormones as well as increasing their effectiveness by implanting tablets of solid material under the skin, the possibility of applying such a technique to nonsteroid hormones such as insulin became obvious. Parkes & Young (104) were the first to report the results of such experiments, finding that in normal rabbits the absorption of 5 mg. pellets of crystalline insulin or of insulin with low zinc content stopped after about twenty-four hours, the pellets of low-zinc insulin having been completely absorbed in this time while those of crystalline insulin had become encapsulated. In both instances the effect on the blood sugar was little different from that of the subcutaneous injection of a solution of a similar dose (100 units) of ordinary insulin. This result was confirmed by Mark & Biskind (105) as far as crystalline zinc insulin was concerned, but these authors further showed that the addition of 20 per cent of protamine to the insulin pellet greatly prolonged the physiological effect of implantation. Cutting, Morton & Cohen (106) introduced the use of tablets containing cholesterol mixed with insulin, and subsequently a number of investigators have used mixtures of

insulin, cholesterol, and other substances (107 to 110) with no very striking success. Experiments have been carried out with the implantation of open-ended silver cylinders containing insulin (108, 109, 110), of insulin adsorbed on powdered carbon (111), and with the introduction of insulin suppositories *per vaginam* (112), but in no instance have the results justified hope that such means of prolonging the action of insulin will ever replace those introduced by Hagedorn and his colleagues, the use of protamine insulin and its congeners.

Action of alloxan on pancreatic islets.—In 1937 Jacobs (113) found that in normal rabbits the intravenous injection of alloxan (mesoxalyl urea) produced a profound hypoglycaemia, accompanied by convulsions which were relieved by the intravenous administration of glucose. This action of alloxan appeared to be highly specific, since dialuric acid, alloxantin, barbituric acid, alloxanic acid, and many other related substances were inactive in this respect. Recently Shaw Dunn *et al.* (114, 115) have independently confirmed these observations, and have further shown that a single intravenous injection of alloxan can cause acute necrosis of almost all the islet tissue in the pancreas of the rabbit. They suggest that this effect, which is also given by 2 (*p*-acetylaminostyryl), 6-dimethylaminoquinoline methochloride, may be the result of excessive stimulation of islet activity, and that the cells finally fail and undergo necrosis because they have been overdriven (115). Another possible explanation of the results of Shaw Dunn *et al.* is that alloxan exerts a purely toxic action on islet cells, which liberate their preformed insulin into the blood stream during the process of rapid necrosis (Hughes, private communication). The pancreas of a 1 kg. rabbit contains more than ten units of extractable insulin (116) and the liberation of this into the blood stream might well account for the hypoglycaemic phase of the action of alloxan. Shaw Dunn and his colleagues have made the very important observation that persistent glycosuria may appear in rabbits¹ and in rats as the result of one or more injections of alloxan, and that many of the treated animals subsequently exhibit the cardinal symptoms of diabetes mellitus, associated with pathological changes in the islet tissue (115). These authors discuss

¹ The induction of persistent glycosuria in rabbits receiving a single intravenous injection of alloxan has been confirmed in the reviewer's laboratory by Dr. L. L. Ware.

the possibility that alloxan may be formed in the body under physiological conditions, and act as a muscle hormone in regulating islet activity. They refer to alloxan as a "possible cause of an initial disturbance of the islet system which may eventuate in diabetes mellitus" (115). Although direct evidence for such a biological role of alloxan is at present lacking, further research on the action of alloxan will almost certainly lead to important advances in our knowledge of the physiology and pathology of the islets of Langerhans of the pancreas.

Diabetes and pancreatic islets.—More than fifty years ago Minkowski and Weintraud made the suggestion that species differences in effects of pancreatectomy are associated with the natural dietary habits of the animals, and that depancreatized carnivorous birds, unlike the duck, the pigeon, and the fowl, would be expected to exhibit glycosuria. Minkowski, Langendorf & Weintraud carried out experiments which supported this idea in so far as the hawk, falcon, buzzard, and raven were concerned, and now Mirsky (117) has added a detailed investigation of the reaction of the carnivorous owl to pancreatectomy, showing that this operation is followed by marked hyperglycaemia and an increased susceptibility to fasting ketosis. Prolonged observations were complicated by the finding that the operated animals lost weight and ultimately died whether or not insulin was administered. The reason for this was not clear, but the influence of pancreatectomy on the blood sugar in this species was unequivocal.

When a depancreatized monkey was allowed to eat after insulin had been withdrawn, only a mild ketosis ensued (118, 119), but deprivation of both food and insulin induced a high degree of ketonaemia. Mirsky's results are thus not in agreement of those of earlier workers (120, 121) who were unable to produce a severely diabetic condition in the monkey by complete extirpation of the pancreas, and who compared the metabolic condition of the depancreatized monkey with that of the depancreatized-hypophysectomized dog.

Barrington (122) has shown that destruction of the glandular follicles present in the wall of the alimentary canal of ammocoete larvae induces a significant rise in the blood sugar level. The follicles exhibited a clear response to the injection of glucose, including extensive vacuolization, and Barrington discusses the possibility that these bodies, which he aptly names "follicles of Langer-

hans," represent a primitive stage in the evolution of the endocrine component of the vertebrate pancreas. From time to time claims have been recorded, but not always substantiated, that blood sugar-reducing fractions can be prepared from duodenal mucosa, while the existence of aberrant pancreatic tissue in the duodenal wall, associated with hyperinsulinism (123) suggests the possible importance and interest of further comparative studies.

In normal adult human beings the pancreas contains 0.9 to 2.7 per cent of islet tissue (124) while the majority of diabetic people have less than 0.9 per cent. On the other hand children may possess as much as 3.6 per cent. Best *et al.* (125) have studied the insulin concentration in the pancreatic remnant of partially depancreatized dogs, and find that the concentration of insulin (units per gm. of fresh tissue) is the same as that in a normal pancreas if enough glandular tissue has been left to prevent the onset of diabetes, but that the concentration falls to a very low level if insufficient tissue is present to prevent hyperglycaemia and glycosuria. A normal concentration was recorded for hypophysectomized-depancreatized dogs. These experiments support the thirty-year old conclusion of Allen that the degenerative changes which occur in the islet cells of the diabetic partially-depancreatized dog result from overstimulation of the insulin-secreting mechanism. Mirsky *et al.* (126) found that the daily administration of protamine zinc insulin to partially depancreatized dogs resulted in the appearance of hyperglycaemia and glycosuria after twenty to forty weeks treatment, at which time the surviving pancreatic remnant was found to contain no normal islet tissue. These authors emphasize the possible dangers of the prophylactic use of insulin.

A blood-sugar raising action of parotid extracts (127) has been recorded in rats, the pancreatic islets of which were found to be somewhat abnormal at autopsy.

An earlier claim (128) that the relative rates of the intracutaneous absorption of glucose and saline in diabetics may differ from those in normal people has been confirmed (129).

THE ADRENAL CORTEX

The literature on this subject continues to grow apace but fortunately during the past year a number of articles summarizing

the literature have been published. These include reviews by Pfiffner (130) on the nature of adrenal cortical hormones, by Thorn (131) on desoxycorticosterone with particular references to clinical practice, by Kendall (132), Hartman (133), and Ingle (134), all of whom have contributed general reviews; by Long and his colleagues (135) on adrenal cortical hypertrophy, and by Verzár (136) on the adrenal cortex and sex hormones.

Physiological activity of cortical compounds in relation to their structure.—If a hydroxyl group is inserted at the 17 position in desoxycorticosterone, the compound so formed—11-desoxy-17-hydroxy-corticosterone—possesses the power to “retain” sodium and chlorine, but is less active in this respect than desoxycorticosterone (137). The introduction of a hydroxyl group into the same position in corticosterone, giving 17-hydroxycorticosterone, converts a compound which retains sodium and chlorine into one which facilitates their excretion (137). Thus the introduction of a hydroxyl group into the 17 position of the cortical-steroid molecule appears to depress the sodium and chlorine retaining activity of these compounds.

As judged by biological tests, extracts of hog adrenal glands contain more cortical steroids with a hydroxyl group in position 11 than do similar extracts from either beef or sheep glands (138). The relatively accessible synthetic compound, acetoxypregnenolone, possesses less than one-sixth the activity of desoxycorticosterone acetate in maintaining the adrenalectomized dog (139).

In contrast to its action in other species desoxycorticosterone acetate does not induce chlorine retention in normal rabbits, when doses are administered which would be expected, on the basis of experiments with other types of animal, to exhibit such activity (140). However, in other species this substance can cause nephrosclerosis (141), cardiac lesions (142), gynecomastia (143), and precocious development of teeth (144). Administration of adrenal cortical extracts does not induce ketosis in the rat, nor are corticosterone or its 11-desoxy- or 11-dehydro-17-hydroxy- derivatives active in this respect (145). Δ^5 -pregnene-3-ol-20-one-21-ol-acetate is able to produce growth and prolong the survival of adrenalectomized rats, its activity falling between that of progesterone and of desoxycorticosterone acetate in this respect (146).

Methods of administering cortical steroids.—Even though desoxycorticosterone acetate is active when administered orally

(147, 148), sublingual treatment of Addison's disease with this substance has not always proved satisfactory (149) and much evidence has accumulated that the subcutaneous implantation of pellets of solid material is an efficient and economical way of treating the condition (150, 151, 152). Thaddea (150) computes that the implantation technique saved him 90 per cent of the amount of active substance required for satisfactory treatment by subcutaneous injection. The belief that inactivation of the hormone in the liver causes pellets of desoxycorticosterone acetate to be less effective if they are implanted into areas drained by the portal circulation (153) has not been supported (154).

The adrenal cortex in relation to conditions of stress.—Thorn and his colleagues (155) have investigated the reaction of the adrenal cortex to the state of acute anoxia induced by lowered barometric pressure in experiments on man and on normal and adrenalectomized animals. They conclude that during the initial phase of anoxia there appears to be an increased utilization of carbohydrate, and a normal blood sugar level is maintained at the expense of the liver glycogen stores. Successful adaptation to continued exposure to low oxygen tension depends in part on an increase in protein catabolism, with a subsequent rise in carbohydrate stores and an increase in nitrogen excretion. These changes appear to depend on the cortex of the adrenal glands as they do not occur in its absence. Acute anoxia is accompanied by a rise in the pH and in the chloride ion concentration of the serum. Prolonged anoxia (lasting twenty-four hours) leads to a substantial increase in the renal excretion of sodium and of chlorine, which appears to be stimulated by the "carbohydrate-regulating" factor(s) of the adrenal cortex, and to an increased excretion of potassium which appears to be accountable largely to factors other than the adrenal cortex. Further experiments (156) revealed species differences (between the rabbit, rat, and dog) in the reaction to low barometric pressure. In rats repeated exposure to reduced pressure was not associated with an accumulation of carbohydrate reserves, such as occurred with a single twenty-four hour exposure, but resulted in a definite reduction in carbohydrate stores. In these animals treatment with adrenal cortical extract afforded some protection against the effects of exposure to a reduced pressure equivalent to a height of 27,000 feet. Although adrenalectomized rats at first required greatly increased doses of cortical extract for main-

tenance during exposure to a pressure equivalent to 20,000 feet, after acclimatization their requirements diminished to that of animals at normal pressure (157, 158). Histological changes, which are apparently related, are observed in the adrenal and pituitary glands of rats exposed to a pressure equivalent to 25,000 feet (159). Silvette (160) records that when rats are exposed daily for three hours to a pressure equivalent to a height of 15,000 feet, such as to produce hypertrophy of the adrenal glands, the daily output of urine is significantly increased, although some degree of acclimatization may occur as far as this change is concerned. Renal hypertrophy was also observed in these animals.

The diversity of opinions regarding the value of adrenal compounds in its prevention or relief is exceeded only by the variations in methods and conditions which have been employed to bring about a condition described as "shock." It has been claimed that some protection is given by treatment with adrenal cortical preparations against "shock" associated with general trauma (161), muscular trauma and hemorrhage (162), venous occlusion (163, 164, 165), low environmental temperature (166), intraperitoneal injections of isotonic, (167) or hypertonic, (168) glucose solution, and with *Cl. Welchii* infection (169). On the other hand, other investigators have had no success with adrenal therapy with respect to experimental hemorrhage (170, 171), trauma resulting from limb ligation (172), experimental anuria (173), and in conditions of surgical shock (174, 175) and of toxic disease (176) in human patients. The only comment that may be permitted at this stage is one of regret that adrenal cortical substances have not fulfilled the hopes that were once entertained of their usefulness in so-called conditions of shock.

Sarason has studied the morphology of the adrenal cortex in the rat (177) and in the human (178) under various conditions. In the hypophysectomized rat treatment with desoxycorticosterone leads to still further atrophy of the adrenal glands (177) so that it may be assumed that in normal animals the atrophic action of such treatment is not necessarily mediated by the hypophysis. Adrenal hypertrophy is usually associated with lipid depletion, though in hypertension (but not in atherosclerosis) adrenal enlargement is accompanied by an increase in lipid content (178).

Adrenal hormones and water balance.—In normal dogs (179,

180) and in human beings (181) the retention of sodium and chlorine induced by daily treatment with desoxycorticosterone acetate is associated with a significant increase in the blood plasma volume. The physiological antagonism between adrenal-cortical extract and pitressin with respect to the excretion of sodium, chlorine, and water has been confirmed in human diabetes insipidus (182). In this condition the cortical extract failed to increase the excretion of potassium unless pitressin was also given. Depression of renal function in Addison's disease, and in chronic adrenal insufficiency associated with panhypopituitarism, can be partially but temporarily relieved by the administration of desoxycorticosterone acetate (183). Treatment with this substance of hypophysectomized rats in which the initial postoperative diabetic condition had subsided, elevated the water exchange, but not to levels characteristic of diabetes insipidus (184).

In the adrenalectomized dog (185) and cat (186) the increase in blood plasma protein content is due to an increase in the globulin fraction. The plasma albumin may remain unchanged or may diminish. Treatment with adrenal cortical preparations increases the plasma albumin level. Levin (187) has shown that in the rat with diminished adrenal function plasma albumin cannot be maintained at the normal level with the depressed food intake characteristic of this condition. Forced feeding can, however, bring the albumin content to a normal value if the food intake is thus maintained at a level much greater than that which obtains when the animal consumes only that food which he will voluntarily eat.

Adrenal cortex and intestinal absorption.—Verzár still maintains his belief that the primary dysfunction in adrenal insufficiency is a diminution in the activity of phosphorylating mechanisms (188), of which a decreased rate of intestinal absorption is but one result. Recent investigations with radioactive phosphorus (189) have failed to demonstrate any deficiency in the phosphorylation of fat in adrenalectomized rats. But the intestinal absorption of fats containing long-chain fatty acids appears to be depressed in such animals (190) although the absorption of tributyrin and of sodium butyrate is unaffected. This suggests that the absorption of long-chain acids, but not of water-soluble fatty acids, may be dependent on adrenal activity. Although the rate of absorption of glucose from the gut of the adrenalectomized rat is depressed, it can be

restored to normal by continued sodium chloride therapy, which suggests that the disturbance in absorption is not hormonal *per se*, but is a consequence of the general disturbance in salt metabolism (191). The inevitable general conclusion to be drawn appears to be that the evidence against Verzář's attractive idea still outweighs that supporting it.

The adrenal cortex and the metabolism of carbohydrate and protein.—In discussing this question Long (192) suggests that although the exact mechanism of action of adrenal cortical hormones on carbohydrate and protein metabolism is not yet clear, two processes seem to be influenced by them—the oxidation of glucose in the peripheral tissues, which is depressed, and the formation of carbohydrate from amino acids, or their residues after deamination, which is stimulated. The view is adopted that excess of cortical hormone given to a normal animal leads to an accumulation of stored carbohydrate by preventing the breakdown of any glycogen originally present, or subsequently formed from dietary carbohydrate or noncarbohydrate precursors. Since their supply of carbohydrate would be blocked by this process, the tissues would be forced to use more protein or fat for combustion. Although adrenal cortical hormones may accelerate the conversion of tissue proteins to amino acids in muscles, in the liver, or in both of these sites, direct evidence on this point is lacking. The increase in potassium and phosphate ion excretion in animals treated with corticosterone is explicable as the liberation of the inorganic salts associated with the cellular protein which is broken down, but as desoxycorticosterone exerts a striking effect on electrolyte excretion without possessing a comparable influence on carbohydrate and protein metabolism, no simple theory can interpret all the changes in inorganic metabolism as a sequence to a primary action of cortical hormones on organic metabolism, although the two are undoubtedly related in part (192). A recent comprehensive review on adrenal cortical hypertrophy leads Tepperman, Engel & Long (135) to suggest that adrenal cortical hormones may act on a substrate derived from the animal's own tissues or from its dietary protein, and that the hormone requirement may be increased, and its secretion stimulated, by the presence of excessive amounts of this substrate in the body. Experiments by the same authors (193), in agreement with those of Sarason (177), show that substantial hypertrophy of the adrenal cortex, associated with lipid

depletion, can occur when rats are given a high protein diet for 4 to 7 weeks. As such hypertrophy was observed with a diet containing 60 per cent casein and 20 per cent carbohydrate, carbohydrate deprivation is presumably not the cause of the adrenal enlargement. The adrenal hypertrophy was associated with an elevation in the fasting blood sugar and liver glycogen levels comparable with that resulting from the administration of potent adrenal cortical extract to animals receiving a normal diet. These experiments support the idea that some event which occurs during the catabolism of protein serves as a stimulus for the hypertrophic response of the adrenal cortex to a variety of conditions. Nevertheless Ingle and his colleagues (194) find that changes in the weights of the adrenal glands of the normal rat and in the period of survival after adrenalectomy, brought about by altering the proportions of carbohydrate, protein, and fat in the diet, are small and probably without significance. As the high-protein diet used by these investigators contained nearly 70 per cent of protein it is surprising that they did not observe the adrenal hypertrophy described by Long *et al.* (193), and no obvious reason for this discrepancy appears from the nature of the diets used by the two groups of workers, although the age of the experimental animals may be one factor of importance. Liver arginase activity is diminished by adrenalectomy in the rat, and increased by the administration of only those steroids which have an oxygen atom or hydroxyl group at position 11 (195, 196) and which therefore exert a substantial influence on carbohydrate metabolism.

Although desoxycorticosterone is not generally believed to exert any substantial effect on carbohydrate metabolism, it has been claimed (197) that mice previously treated with repeated 2 mg. doses of this material are resistant to the convulsive action of insulin. The rate of absorption of relatively water-insoluble active substances may be a factor of importance in such experiments. The action on creatine excretion and carbohydrate metabolism of water-soluble preparations of desoxycorticosterone emphasizes this point (198). Reinecke & Kendall (199) have devised a widely-adopted method for the bioassay of adrenal-cortical hormones which increase hepatic glycogen deposition.

The metabolic changes in a patient with Addison's disease who subsequently developed diabetes mellitus suggest that the inability of patients with uncomplicated Addison's disease to maintain the

blood-sugar level during fasting is not due only to deficiency of adrenal-cortical hormones (200). Nevertheless in this diabetic patient the experimental injection of only 33 mg. of 11-dehydro-17-hydroxy-corticosterone produced a rise of blood sugar, a lowering of the nonprotein respiratory quotient together with increased excretion of glucose, nitrogen, phosphorus, sodium, and chlorine, and the appearance of ketonuria. A case has been recorded (201) of a woman in whom a severe disturbance of carbohydrate metabolism, which had the characteristics of diabetes mellitus and which was unaccompanied by other endocrine abnormalities, disappeared completely following the removal of an adrenal-cortical tumor.

Urinary excretion of cortical steroids.—According to Dorfman and his colleagues normal human urine contains cortical steroid-like material which, when administered to adrenalectomized rats, protects them against death from cold (202), increases their fasting liver glycogen stores (203), and maintains life (204). A normal person excretes each day the equivalent of 0.15 to 0.18 cc. of Wilson adrenal cortical extract, but no activity is found in the urine of patients with Addison's disease (202). Browne *et al.* (205) have shown that the cortical steroid-like material present in the urine of patients after operation also possesses gluconeogenic and life-maintaining properties.

When desoxycorticosterone is administered to normal rabbits the equivalent of 5 to 20 per cent can be recovered from the urine as pregnanediol (206, 207). Although similar observations have been made with human males (108) more recent observations on human beings receiving physiological doses of desoxycorticosterone acetate gave no evidence of its conversion to pregnanediol (209).

THE ANTERIOR PITUITARY GLAND

Two general reviews on this subject have recently appeared (210, 211), and during the period under consideration two reviews by Long (212, 213) dealing with the influence of the pituitary gland on growth and metabolism have been published.

Physiological action of growth hormone.—Evans and his colleagues have obtained pituitary growth-promoting preparations which are essentially free from thyrotropic, lactogenic, and adrenocorticotrophic hormones (214). Other evidence differentiates the growth hormone from the pituitary ketogenic factor (215, 216,

217). Methods of bioassay of the growth hormone are becoming standardized (218, 219, 220; see also 221), although in every species of animal an increase in body weight is not necessarily observed on treatment with preparations which are potent in this respect in rats. Giles (222) found that increased calcification of the bones was the chief result when young pigs were given intraperitoneal injection of growth hormone twice weekly for four and one-half months. The appetite of hypophysectomized rats increases when they are treated with growth-promoting anterior pituitary extract, but if their food intake is restricted to that of control animals, injection of growth hormone still succeeds in inducing an increase in weight (223). Thus the pituitary gland stimulates a more efficient formation of body material from ingested foodstuff in rats. Incidentally the increase in size thus induced does not alter the symmetry of the animal (224).

According to Evans and his colleagues, purified thyrotropin does not itself possess a growth-stimulating action, although it exerts a true synergism with growth-promoting pituitary extracts in the hypophysectomized rat (225). In both normal and hypophysectomized rats the blood amino acid content is reduced by treatment with growth hormone and with thyrotropin, but not with thyroxine (226). As the influence of thyrotropin is undiminished after removal of the thyroid, its action is presumably not mediated by that gland. In normal rats growth hormone does not lower the blood urea content, and has an insignificant effect on the high blood urea of the hypophysectomized animal, but in both instances the amount of urea in the blood is strikingly diminished by thyrotropin and by thyroxine. In the thyroidectomized rat thyrotropin has a doubtful lowering action on the blood urea, while the action of thyroxine is also small and not statistically significant. The authors tentatively conclude that thyrotropin lowers blood urea by a direct action, as well as through the mediation of the thyroid secretion which it calls forth, but that it reduces the blood amino acid concentration by direct action only. As, in these experiments, the diminution in blood urea was not the result of increased elimination of urea, nor was it due to hemodilution, it presumably resulted from diminished production of urea in the liver (226). As was thus to be expected, purified thyrotropin reduces the urinary nitrogen excretion of the normal rat, though not to the same extent as does growth hormone (227). Other hor-

mones which were without significant effect on urinary nitrogen excretion under the conditions employed by these investigators included thyroxine, adrenal-cortical extract, and protamine zinc insulin (227).

As a natural corollary to these important investigations Evans and his colleagues have investigated the effect, on enzyme systems concerned with the production of urea, of alterations in hormonal influence, and for this purpose have studied the activity of liver arginase under a variety of conditions (228). Hypophysectomy in rats leads to a substantial diminution in liver arginase activity (228) while adrenocorticotropin, which increases the blood urea (226), also increases the arginase activity of the liver both of normal (195) and of hypophysectomized rats (228). In contrast to this, the growth hormone, which has no significant effect on the level of urea in the blood, diminishes the arginase activity in the livers of normal and of hypophysectomized rats (228). This diminution is particularly interesting in view of the somewhat surprising earlier finding that treatment with growth hormone causes only a slight absolute increase, representing a significant relative decrease, in the weight of the liver of the hypophysectomized rat (229). It appears that the anterior pituitary gland exerts opposing actions on liver arginase activity; growth hormone diminishes the activity, while adrenocorticotropin, mediated by adrenal cortical hormones (195, 196), increases it. The effect of removal of the pituitary gland in inducing a diminution in liver arginase activity, a diminution which is not so great as that which follows adrenalectomy (196), is explicable (228) on an assumption which is in keeping with the experimentally determined quantitative relationships, that the normally functioning pituitary gland does not secrete enough growth hormone to neutralize the stimulating effect on the activity of the liver arginase, of its own adrenocorticotropin. On the other hand, growth hormone will stimulate growth in the rat in doses which are considerably lower than those required to produce a significant change in the liver arginase activity, so that it is possible that the diminution in arginase activity in response to larger doses of growth hormone is secondary to a diminished need for this enzyme. Such a diminished need would be expected in animals with a positive nitrogen balance, in which tissue protein may be in the process of construction from dietary amino acids which are thus escaping deamination in the liver.

The adrenal cortex and pituitary influence on protein metabolism.—Although, immediately after hypophysectomy in the rat, there may be an increased excretion of nitrogen in the fasting state, sometime after the operation the nitrogen excretion is found to be reduced, as in the adrenalectomized animal. This diminution may be due in part to the adrenal atrophy which occurs as the result of the operation (230, see also 231). Adrenal steroids will not induce growth in the hypophysectomized rat (232) and pituitary extracts will cause growth in adrenalectomized rats which are not receiving treatment with adrenal cortical hormones (230), albeit the response to the pituitary extract is better if adrenal extract is also administered. Thus it seems that the lack of growth in the hypophysectomized rat and failure of this animal to retain nitrogen under conditions in which the intact animal readily does so are not merely the result of a diminished supply of adrenal-cortical hormones, while, conversely, the pituitary growth hormone is not dependent for its action on the cooperative secretion by the cortex of the adrenal glands of its physiologically active steroids. Furthermore Gaebler has shown that anterior pituitary extract can induce some retention of nitrogen in a dog lacking thyroid, pancreas, and both adrenal glands (233, 234). In such an animal a moderate degree of nitrogen retention and some increase in body weight is observed when, during a period of constant diet and daily injections of insulin and cortical extract, a pituitary growth preparation is administered.

Long and his collaborators (135, 193) suggest the possibility that adrenal cortical hormones may be used up in bringing about the catabolism of a substrate derived from protein, exogenous or endogenous, and that a fall in the concentration of the adrenal hormones in the body fluids releases from inhibition the secretory activity of the anterior hypophysis with respect to adrenocorticotrophic action. Such views, and the results of investigations on liver arginase activity (195, 196, 228) emphasize the catabolic action of adrenocorticotrophic function in relation to protein metabolism. Nevertheless, as Long (230) has pointed out, the growth-promoting activity of pituitary extracts is not fully manifest in the absence of proper adrenal-cortical cooperation, although some growth can be induced in the total absence of adrenal hormones. Likewise, pituitary diabetogenic action, which entails protein catabolism, may be diminished in adrenal insufficiency, although

some diabetogenic effect of anterior pituitary extract is demonstrable in adrenalectomized dogs maintained with sodium chloride alone (235). The fact that a process which stimulates protein catabolism appears to form a constituent part of the pituitary complex responsible for the full growth-promoting and nitrogen-retaining action of crude anterior lobe extract is an interesting example of the duality of many biological systems, which may be constituted from two (or more) balanced reactions. Divorced from the system of which they form an integral part, such processes are often completely opposing in their ultimate effects, although both are essential for the full manifestation of activity in the system as a whole. It is clear that the opposition of such reacting processes provides a simple mechanism for the maintenance of the system in delicately-controlled equilibrium.

The relation of the pancreatic islets to the growth-promoting and diabetogenic actions of the anterior pituitary lobe.—On numerous occasions Young (236 to 242) has emphasized the relationship between the growth-promoting and diabetogenic actions of anterior pituitary extracts, the latter effect being that demonstrable in intact animals. Although pituitary extracts were obtained which stimulated the growth of normal rats without being able to induce the appearance of glycosuria in dogs (239, 240), it was not found possible to prepare pituitary extracts which were diabetogenic in the intact dog but which were without growth-promoting action in intact rats (236 to 240). More recently Evans and his colleagues (243) have reported that the administration of purified growth hormone preparations to partially depancreatized rats leads to an increase in glycosuria. The growth-promoting preparations used were practically free from lactogenic hormone, adrenocorticotropin, and thyrotropin. Earlier Young (240) had shown that pituitary preparations could be obtained which were without diabetogenic effect in intact dogs and which induced nitrogen retention and a diminution in D/N quotient when administered to mildly though permanently pituitary-diabetic dogs. Such preparations, however, greatly exacerbated the diabetic condition of more severely diabetic animals. Young suggested that the diabetogenic or diabetuaxetic (diabetes intensifying) action of the extract was masked or converted into a growth-promoting action in animals in which sufficient insulin was available for secretion from the pancreatic islets in response to the pituitary treatment. The ob-

servation of Evans (243) that highly purified preparations of growth hormone, which produce growth and not diabetes in intact rats, induce an increase in the diabetic condition of partially depancreatized rats appears to be in concord with this idea. Young (240) found that when young puppies were treated daily for long periods with diabetogenic pituitary extract they did not exhibit glycosuria, as did adult dogs, but rapidly increased in body weight like the animals in the classic experiments of Evans. After many months of treatment diabetes did ultimately develop in some of these animals (244) and thereafter the pituitary extract had lost its growth-promoting action and merely exerted a diabetogenic or diabetauxetic action. One animal, however, was induced to resume growth when insulin was given together with the pituitary extract, but more than 2,000 units per day of protamine zinc insulin were insufficient, at this stage, to control the glycosuria induced by the same daily dose of anterior pituitary extract as had exerted only a growth-promoting action during the animal's younger days. It seems unlikely that during the period of growth the pancreas of this animal had secreted each day the equivalent of more than 2,000 units of insulin, but nevertheless it is improbable that some cooperative secretion of insulin had not been necessary during the time that the diabetogenic action of the pituitary extract was completely masked and the extract thus rendered growth-promoting. As the result of his carefully controlled experiments in which depancreatized dogs receive a constant daily dose of insulin, Gaebler (233) lends support to the idea that whether an anterior pituitary preparation will cause nitrogen storage or diabetogenic effects may depend on the amount of insulin that the pancreas can supply, but he concludes that his experiments show that additional insulin is not the only factor which operates to prevent interference with the proper utilization of carbohydrate when pituitary extract is administered.

Best *et al.* (245) have shown that the daily administration of insulin to normal dogs which are undergoing treatment with diabetogenic pituitary extract tends to prevent the reduction in insulin content of the pancreas, and the degranulation and hydropic degeneration in the β -cells of the islets of Langerhans, which follows injection of the pituitary extract alone. The authors interpret their results as providing confirmation for the theory that the anterior pituitary extract damages the β -cells by stimulating them to over-

work. They suggest that the insulin may exert its protective action either by reducing the blood sugar level or by raising the level of insulin in the blood. Houssay *et al.* (246) measured the rate at which the pancreas of an experimentally treated dog is secreting insulin by uniting the circulation of this organ with that of a second, depancreatized dog, and determining the rate at which the blood sugar level of the recipient animal falls. Treatment with diabetogenic extract for four days produced a marked diminution in the capacity of the pancreas to secrete insulin, with histologically demonstrable degenerative changes on the islet cells. If, however, a normal dog received a continuous and prolonged intravenous infusion of glucose of such intensity that the blood sugar level was maintained for four days at a level similar to that observed in dogs made diabetic by anterior pituitary treatment, its pancreas retained the normal capacity to secrete glucose. Histologically the β -cells in the pancreas of such an animal were hyperplastic rather than degenerate, and there were signs of hyperfunction. The authors conclude that the anterior pituitary extract induces degenerative changes in the islets, and a diminution in the capacity of the pancreas to secrete insulin, by a mechanism other than that of raising the blood sugar by extrapancreatic means, although the high blood sugar level probably exhausts the β -cells and exaggerates their injury. They consider that the pancreatic islets are damaged by a direct action of the anterior lobe extract on the islet cells, and that the hyperglycaemia produced by other means aggravates the islet lesions produced by this direct action. The nature of this direct action is not at all clear, and most other workers have assumed that the damage to the islets is more likely to be the result of the high blood sugar level. The experiments of Shaw Dunn with alloxan (114, 115) discussed above, show, however, that pancreatic islet lesions can be produced very rapidly under some conditions, without the mediation of hyperglycaemia, and it may well be that in accordance with Houssay's views, the diabetogenic pituitary extract exerts a direct degenerative action on the pancreatic islet cells. At present, however, no final conclusion can be drawn as to the mechanism whereby the lesions are produced.

As well as producing degenerative changes in the pancreatic islets, anterior pituitary extracts exert a pancretotropic hyperplastic action on the islet tissue (239, 245, 246), so that again two

antagonistic actions of the anterior pituitary lobe appear to be associated. In this case hypophysectomy in mammals results in hyperplastic rather than degenerative changes in the pancreatic islets, but Miller (247) has recently reported that in the pigeon hypophysectomy or underfeeding causes degeneration of the β -cells. As with mammals, various anterior lobe extracts will cause stimulation of the pancreatic islets of the pigeon (247). It is interesting to note that the development, with advancing age, of destructive changes in the pancreas of the rat have recently been described (248, 249) which may well be associated with the appearance of senile changes in the anterior pituitary lobe demonstrable in this species (250, 251). Such observations and others concerned with pancreatic function in young animals (124, 240, 244) may serve to emphasize the importance, during a period of growth, of the adequate supply of pancreatic insulin in relation to pituitary growth-promoting action.

The anterior pituitary gland and insulin sensitivity.—Although previously there has been some doubt on this point two groups of workers have recently agreed that the postabsorptive blood sugar level of the hypophysectomized dog is significantly lower than that of the intact animal (252, 253, 254). Loss of either the posterior or the anterior pituitary lobe has, in the dog, no influence on the sugar tolerance, as demonstrated by the response to oral or to intravenous glucose, although in the absence of the pituitary gland there may be an exaggeration of the phase of hypoglycaemia which normally follows the hyperglycaemic response to the administration of carbohydrate (252).

De Bodo *et al.* (253, 254) have reopened the question of the influence of the anterior hypophysis on the response of the liver to glycogenolytic agents. They have shown (253) that in the hypophysectomized dog the slow intravenous infusion of epinephrine, at a rate which is effectively hyperglycaemic in the normal animal, produces only a slight rise in blood sugar level, despite the presence of ample stores of liver glycogen in the animal without pituitary. Fasting normal dogs, with much smaller stores of liver glycogen than are found in the hypophysectomized animal, give a much greater hyperglycaemic response to intravenous epinephrine than do the operated animals, although dogs from which only the posterior lobe of the pituitary gland has been removed react normally. These results are in contradistinction to

those of Russell & Cori with the rat, but they agree with those of Braier and confirm the view, put forward by Cope & Marks and emphasized by Képinov and others, that an important defect in the hypophysectomized animals is the resistance of the glycogen stored in the liver to the action of glycogenolytic agents which are effective in the normal animal, and that this defect accounts, at least in part, for the increased sensitivity to insulin and liability to dangerous hypoglycaemia on sustained fasting in the animals lacking a pituitary gland (255).

De Bodo has (254) emphasized the fact that extreme adrenal atrophy is characteristic of the completely hypophysectomized dog, but that there is no reason to believe that the adrenal medulla is incapable of secreting its hormone in such an animal. The medullary cells are hypertrophic rather than atrophic, and their condition is suggestive of great secretory activity (256).

The postabsorptive blood sugar level is determined by the relative rates of glucose production in the liver and glucose utilization in the tissues generally. De Bodo (254) points out that even if the tissues of the hypophysectomized animal are utilizing glucose at twice the normal rate (257) such an increased utilization would not necessarily account for the excessive tendency to post-absorptive hypoglycaemia in the absence of the pituitary gland. Intact dogs are capable of maintaining a normal blood sugar level during sustained muscular exercise in the postabsorptive condition, during which the glucose utilization may rise to four times the normal value. If the sugar-producing mechanism in the liver of the intact animal can maintain a normal blood sugar level despite a quadruple increase in glucose utilization, there is no reason why the doubling of glucose utilization which may follow removal of the pituitary gland should entail a tendency to hypoglycaemia, unless the rate at which sugar can be produced in the liver of the hypophysectomized animal is depressed. The results of de Bodo and his colleagues appear to provide a strong argument against the simplified ideas of those who would account for the hypoglycaemic tendencies characteristic of the absence of the pituitary gland as primarily or solely the result of increased glucose utilization. It is perhaps not inopportune to recall that some years ago Crandall & Cherry (258), by direct determination of the blood sugar levels in the blood flowing to and from the liver in unanaesthetized angiotomized dogs, were able to show that the output of glucose by the liver of the hypophysectomized dog

averages less than 50 per cent of that in the normal animals and that the output does not increase during insulin hypoglycaemia as it does in intact dogs. Hypophysectomized dogs showed a lack of hepatic response to insulin similar to that exhibited by animals in which the adrenal medullary mechanism had been completely eliminated. These authors carefully consider the question of hepatic blood flow in their experiments, and conclude that the differences in blood sugar level do represent real differences in total sugar output by the liver. In any case it seems most improbable that the blood flow through the liver of the hypophysectomized dog is twice that in the intact animal, and it appears to the reviewer that these results of Crandall & Cherry do provide a legitimate and direct demonstration of the principles which the more recent experiments of de Bodo also emphasize.

Jensen *et al.* (259) have shown that although various urinary preparations induce an elevation in blood sugar level and insensitivity to the hypoglycaemic action of insulin when administered to normal rabbits and mice, such preparations do not necessarily bring about an increase in the liver glycogen content under the experimental condition in which pituitary anti-insulin extracts significantly promote the deposition of glycogen in the liver. These authors therefore distinguish between a specific and a nonspecific anti-insulin (glycotropic) effect of their preparations.

Although an anti-insulin effect has been demonstrated experimentally with blood plasma from some cases of insulin-insensitive human diabetes mellitus such demonstrations are rare and a case of diabetes has recently been described requiring 3,000 to 4,000 units per day of insulin (260), in the blood of which no anti-insulin factor was demonstrable. On the other hand it has been claimed that in certain cases of diabetes (261) and during insulin hypoglycaemia (262) the blood possesses adrenocorticotrophic activity. Such activity would be expected, on the basis of previous work, to endow the blood with anti-insulin activity, though this was not determined.

The claim (263) that the blood of patients with schizophrenia contains an anti-insulin substance, has received some support (264) as well as the converse (265). The intravenous sugar tolerance curve is normal in manic-depressive psychosis (266), this fact emphasizing the dangers of assuming an abnormality in carbohydrate metabolism on the basis of a prolonged blood sugar response to the oral administration of sugar.

The adrenocorticotrophic influence of the anterior pituitary lobe.—Barkay (267) has reported on the histological changes which occur in the adrenal cortex of the hypophysectomized dog. Two months after operation marked degenerative changes are observed in the zona fascicularis, but after four or five months restitutive changes may occur which depend for their development on the presence of the thyroid gland.

A highly purified preparation of adrenocorticotropin has been obtained, which exhibits no obvious growth-promoting, lactogenic, or thyrotropic activities (258). The administration of such a preparation to normal rats lowers the cholesterol content of the adrenal glands within three hours of injection, but repeated injections for three days results in a rise in cholesterol content to above that found in control animals (269). The possibility is considered by the investigators that variations in the cholesterol content of the adrenal reflect changes in the concentration of the steroid hormones in this gland. Injections of purified adrenocorticotrophic preparations into normal mice result in a diminution in weight of the inguinal, axillary, and mesenteric lymph nodes and of the thymus, but the weight of the spleen is unaltered (270). Anterior pituitary secretions increase the resistance of rats to low environmental temperature only if the adrenals are intact (271), and the belief that this pituitary action is mediated by the adrenal glands is strengthened by the fact that the administration of adrenocorticotropin increases the resistance of hypophysectomized and of normal rats to cold, starvation, or anoxia (272), and to the shock produced by intraperitoneal injection of hypertonic glucose solution (168). The finding that injections of adrenocorticotropin afford some protection against shock in adrenalectomized rats (168) is explained on the assumption that the hormone stimulates accessory adrenal cortical tissue, which may be present in the rat. The related changes in the pituitary and adrenal glands of rats exposed to low barometric pressure (159) have been considered above. The role of the pituitary gland and of adrenocorticotropin in the hypertrophy of the adrenal glands which follows exercise in the rat has recently been emphasized (273). The fall in serum albumin content in hypophysectomized rats, which is prevented by forced feeding, is probably related to diminished adrenal function in these animals (187). Although some pituitary hormones may be present in normal human urine no evidence was found for

the presence of adrenocorticotropin therein (274). A case of Cushing's syndrome has been described (275) in which no pituitary basophilic adenoma or hyperplasia was found, but in which adrenal cortical hyperplasia was present.

The thyrotropic influence of the anterior pituitary lobe.—The influence of dietary goitrogenic substances in relation to the thyrotropic action of the anterior pituitary gland (39, 40, 41, 45) has already been discussed. The thyroid glands of dogs which have been hypophysectomized many months previously contain more iodine and thyroxine-iodine than those of normal or of incompletely hypophysectomized dogs, and the glandular tissue shows a greater activity in accelerating metamorphosis in tadpoles (276). It is to be presumed that in the complete absence of hypophyseal secretions, the thyroid can store, and possibly produce, thyroxine-containing colloid.

The admixture of thyrotropin with testicular diffusing factor diminishes its effectiveness (277) as determined by its action on the chick thyroid gland (278). This is attributed to an increase in the rate of absorption and elimination of the subcutaneously administered material, as such an increase would be expected to diminish the physiological effectiveness of the injected active substance. Injected thyrotropin is rapidly eliminated from the blood (279). Such a diminution in effect provides an apt contrast to the increase in effectiveness of material which is administered in the form of subcutaneously implanted pellets of solid substance.

The action of thyrotropin in bringing about a diminution in blood cholesterol content is not abolished by removal of the thyroid gland in the rabbit (280), so that the action cannot entirely be mediated by thyroid secretions.

The anterior pituitary lobe and mineral metabolism.—Although parathyroid function may be largely unimpaired in the absence of the pituitary gland (55) it is well substantiated that anterior pituitary extracts exert a considerable influence on bone formation. By means of careful balance experiments Krishman (281) has demonstrated that the administration of growth hormone preparations to normal rats and guinea pigs results in calcium retention, largely at the expense of the fecal excretion of this material. In these experiments the urinary calcium levels of the treated animals showed no marked or constant differences. The administration of growth hormone to normal mice and to guinea pigs induces

a temporary stimulation of proliferation of epiphyseal cartilage associated with a shortening of the growth period (282). This is followed by premature onset and acceleration of the course of age changes, such as degeneration, and calcification and breakdown of cartilage. The pituitary extract appears to promote both bone formations and bone resorption (282).

In an extensive study of the effect of thyroxine, and of anterior pituitary growth hormone, on endochondral ossification, Evans and his collaborators (220, 283) demonstrated that endochondral ossification is extremely active in normal rats treated with growth hormone, an effect which was still demonstrable in thyroparathyroidectomized rats. The balance between cartilage and bone formation that was finally established in these animals favored the former. Injections of growth hormone plus thyroxine into normal female rats resulted in a greater response in body weight and length than was obtained with growth hormone alone (282, cf. 30, 32, 33); endochondral ossification, although active, was more mature in type in such animals (283). The administration of thyroxine to thyroparathyroidectomized rats caused the bones to return to a normal condition, but such treatment was not effective in thyroparathyroidectomized-hypophysectomized animals unless growth hormone was administered as well as thyroxine. Such combined therapy did repair the growth defect in these animals (283). The results of these extensive experiments emphasize the fact that anterior lobe hormones exert some action on bone formation which is not mediated by the thyroid or by the parathyroid glands, although, in addition, an indirect influence by way of the secretions of these glands is probable. When hypophysectomized rats receiving treatment with pituitary growth hormone were given radioactive strontium, in the form of strontium lactate, by intraperitoneal injection, they deposited the same amounts of the strontium in the femur and mandible as did rats which received no growth hormone (284). The lack of effect of growth hormone in this connection is interesting and significant.

The daily administration to rats of growth-promoting pituitary extract produces bones which are bigger and proportionately stronger than those of control animals, but there is no alteration in the breaking stress of the bony material laid down (285).

The anterior pituitary gland and Simmonds' disease (anterior panhypopituitarism).—Simmonds' disease is no exception to the

rule that a clinical syndrome becomes more easily recognized, and therefore appears to be more common, when experimental investigations have revealed the nature of the derangements of function concerned, and have suggested possible means of treatment. Escamilla & Lissner (286) have listed 595 cases, which include nine described for the first time. They discuss in some detail the symptoms and means of identification of the condition. At least a dozen further cases have been reported (287 to 296). Methods of treatment for which success has been claimed include implantation of tablets of desoxycorticosterone and testosterone and thyroid administration (289), grafting of calf (290) and of foetal (291) pituitary tissue, and administration of testosterone (292) or of methyl testosterone (293).

Miscellaneous observations regarding the function of the anterior pituitary gland.—Investigations on the influence of dietary variations on the rate at which different foodstuffs are utilized by normal and by hypophysectomized rats (297, 298) show that little difference is found when the two groups of animals receive similar high-carbohydrate or high-fat diets, except that the average metabolic rate of the hypophysectomized carbohydrate-fed rats is about 18 per cent below that of the control animals. The operated rats store less body water and liver fat, and more peripheral fat, than do normal animals. It is concluded that the metabolic disturbance in hypophysectomized rats is not with respect to their ability to use any one of the foodstuffs, as long as it is available in proper form in the liver and circulation. The fundamental disturbance is in the mobilization of endogenous stores, both of protein and of fat. Adjustment of either a normal or a hypophysectomized rat to a high-fat diet before a period of fasting increases the rate of fat utilization, and decreases that of carbohydrate, during the days of fast (298). When daily injections of crude anterior lobe extract were given to normal rats on different diets (299, 300) the extract always diminished protein catabolism and stimulated the oxidation of nonprotein nutrients. As the increase in the rate of oxidation of the latter was quantitatively greater than the diminution in the former the total heat production was increased (300).

Hypophysectomy has only a very slight influence on the ability of the rat to remove fructose from its blood (301), the lack of a profound effect being more impressive than the slight change observed. Hypophysectomy in rats, performed six to ten days after

bilateral lesions, not involving the hypophysis, had been placed in the hypothalamus, did not modify the onset and course of obesity which normally follows such a hypothalamic injury (302).

According to Dragstedt and his co-workers (303) the hypophysectomized-depancreatized dog develops a fatty liver in the absence of therapy with pancreatic preparations such as lipocaic just as quickly as the depancreatized dog, and is equally sensitive to the influence of lipocaic in preventing or curing the accumulation of fat in the liver. According to these workers the parenteral administration of lipocaic to guinea pigs prevents the accumulation of fat in the liver which normally follows the administration of ketogenic pituitary extract to fasting animals, and also diminishes the fatty infiltration of the liver which occurs during simple fasting (303). Both hypophysectomy and pseudohypophysectomy (underfeeding) diminish the concentration of ascorbic acid in various organs, including the adrenal glands (304, 305, 306). Pituitary treatment restores the concentration of ascorbic acid in the adrenal glands (305, 306).

Hypophysectomy has no influence on the rate of epithelization of skin wounds, and of fibroblastic repair of stomach wounds, in rats (307). Conversely, treatment with growth-promoting pituitary extract does not influence the rate at which the healing occurs of wounds produced by the removal of skin from the upper thighs of rats (308). The anaemia which occurs in rats after hypophysectomy is susceptible to treatment with many different hormones (309) and does not appear to result from the lack of a specific pituitary factor or hormone. Although thyroxine can bring the blood picture back to normal in the hypophysectomized rat, other hormones (e.g. testosterone, adrenal cortical extract, and desoxycorticosterone) are effective without raising the oxygen consumption and without altering the histological picture of the thyroid gland. It is concluded that the action of some hormones in stimulating erythropoiesis in the hypophysectomized rat, is not mediated by the thyroid secretions (309). The suggestion has been made that the clinical association of pernicious anemia and pituitary insufficiency may be significant (310). The fact that endocrine disturbances may be possibly implicated in the genesis of this type of anemia is supported by its association with hyperthyroidism and with pregnancy (310).

In the dog loss of the anterior lobe of the pituitary gland is fol-

lowed by a reduction of 50 per cent or more in diodrast and inulin plasma clearances, which is attributable to a decrease in renal blood flow (311). There is also a diminution in the maximum tubular excretion of diodrast at high plasma levels, indicative of a depression of renal tubular excretory capacity. These changes, which are not observed in the animal lacking only the posterior lobe of the gland, are not accompanied by a significant change in blood volume. It is therefore believed that the anterior lobe of the pituitary gland exerts a humoral influence on the excretory capacity of the kidney (311). There is evidence that the eosinophil cells of the anterior hypophysis are responsible for the secretion of the agent concerned (312).

Hypertrophy of the harderian glands of the eye, with lipid secretion from the cells of the secretory epithelium, has been observed in guinea pigs, normal or thyroidectomized, receiving anterior lobe extracts (313). When dogs which were receiving treatment with crude anterior pituitary extract were given sodium benzoate at a time when the animals were not excreting sugar, the excretion of benzoylglucuronic acid in the urine was associated with the urinary excretion of glucose (314). A case has been described in which the coexistence of pituitary dwarfism, diabetes mellitus, and a high basal metabolic rate was believed to be associated with the urinary excretion of thyrotropin (315).

The association of the hormonal system with vitamins has again arisen in connection with the development of a cystic pituitary gland in young cattle suffering from vitamin A deficiency (316).

THE POSTERIOR PITUITARY GLAND

Investigation on the preparation and nature of the hormones of the posterior lobe of the pituitary body has recently been reviewed by Irving & du Vigneaud (317). Although a protein, which is probably pure and which possesses pressor, oxytocic, and anti-diuretic activities in constant proportions, has been isolated from the posterior pituitary lobe, the tentative conclusion that this is a hormone of the posterior lobe which possesses multiple activities cannot yet be given unqualified acceptance, and although the available evidence is in favor of such an assumption the question requires still further investigation. It is certain that the highly potent pressor and oxytocic fractions now available represent fairly

pure preparations of separate molecules which may be similar chemically (317). Such fragments might be formed by the splitting of a single hormone molecule which originally possessed multiple activities.

The biological standardization of posterior pituitary hormones has again been under review (318). Dale has discussed the new international standard for posterior pituitary activity, which is about 15 per cent stronger than the old standard, and has described the distribution of international biological standards in war time (319).

The posterior hypophysis and water metabolism.—A micro-method for the biological assay of the antidiuretic posterior lobe factor has been devised (320) by which 0.00002 unit is detectable. Ham (321) confirms the earlier prediction by Silvette (322) that pituitrin solutions may be assayed more accurately and reproducibly by determining their ability to facilitate the urinary excretion of chloride ion, than by measuring their antidiuretic activity. The physiological antagonism between adrenal cortical extract and pitressin with respect to the excretion of sodium, chlorine, and water, has been confirmed in a human subject with diabetes insipidus (192). The antidiuretic substance in the placental tissue and urine of patients with toxæmia of pregnancy can be differentiated from the antidiuretic principle of the neurohypophysis by the fact that, unlike the pituitary substance, it does not promote the urinary excretion of chlorine (323). The two substances also differ in physical properties. The observation that the excretion of the urinary antidiuretic principle in dogs is unaltered by the production of experimental renal hypertension (324) does not cast light on the question of whether or not posterior pituitary function is altered in this hypertensive condition. The urine of rats which have received posterior lobe extract intravenously contains detectable amounts of antidiuretic substance, as demonstrated by administration to other rats (325). According to Fraser (326) separated oxytocic preparations may be more active than pressor extracts in increasing the excretion of water and of chlorine in nonhydrated rats. The diuretic action of the oxytocic preparation was antagonized by the pressor extract both in hydrated and in nonhydrated rats. The oxytocic extract was extremely active in diminishing the excretion of inorganic phosphate, and the author discusses the possibility that these activities with respect to urinary elimination are properties of the oxytocic hormone itself,

and are of physiological significance (326). Fraser has reinvestigated the claim of Heller (327), which was based on the differential destruction of the pressor and antidiuretic activities of posterior lobe extracts at different pH values, that the antidiuretic and pressor pituitary actions are associated with two chemically different substances. Fraser (328) confirmed Heller's observations that, if antidiuretic activity is determined by Burn's method which involves subcutaneous administration of the extract to rats, the ratio of antidiuretic to pressor activity in the chloretonized dog is increased by mild hydrolysis of the pituitary extract. Similar results were obtained when antidiuretic activity was assayed by subcutaneous administration to dogs, but if, for the purpose of antidiuretic assay, the extract was administered to the dog by the intravenous route, hydrolysis was found to have no effect on the ratio of the two activities. Fraser concludes that the partial inactivation of the pituitary extract by hydrolysis involves no real change in the ratio of antidiuretic and pressor activities (328). These results appear to be of some general significance with respect to those claims and to have demonstrated the nonidentity of pituitary hormones, which are based on differential inactivation of active principles.

The influence of pressor extracts on the vessels in the frog kidney has been determined by direct observation with transillumination (329). The circulation in the glomerular tuft was stopped for times varying from a fraction of a minute to several minutes, according to the dose of extract. The circulation in other vessels was markedly slowed. In dogs simultaneous records of urine flow, renal blood flow, and of blood pressure showed that the intravenous administration of pressor extract produced transient anuria, followed by oliguria for several minutes, and a diminution in renal blood flow; recovery was not complete for one-half to one hour (329). There was a sudden transient rise in blood pressure after injection of the extract, sometimes followed by a transient fall and generally succeeded by a gradual, prolonged but moderate rise which lasted for fifteen minutes.

More than twenty years ago Brunn showed that with frogs kept in water the injection of posterior pituitary extract induces a significant increase in weight, attributable to an accumulation of water in the body of the animal. This water was acquired, at least in part, by absorption through the skin. It is only comparatively recently that the nature and mode of action of the posterior

pituitary principle responsible, which for convenience we may call the Brunn principle, has been subjected to serious investigation. Heller has shown that both the mammalian antidiuretic substance (330) and the Brunn principle (331) are present in the pituitary glands of mammals, birds, amphibians, and fishes, and both are also present in the hypophysis of at least one species of reptile (332). In mammals the pituitary gland contains large quantities of antidiuretic substances, the reverse being true for such lower vertebrates as birds, amphibians, and fishes (331). Pituitary glands from different species of the same class of vertebrate contain roughly the same amount of antidiuretic substance for each 100 gm. of body weight, but mammalian pituitary bodies contain at least eight times as much antidiuretic principle (per 100 gm. of body weight) as the glands from any nonmammalian species (330). Heller suggests (330) that a relationship exists between the phylogenetic development of Henle's loop in the kidney and the amount of antidiuretic substance produced by the posterior pituitary lobe, thus correlating the development of an anatomical structure with that of a hormonal mechanism. No such simple relationship is yet recognized with respect to the Brunn principle. As the ratio of antidiuretic substance to the Brunn principle varies so widely among the different species examined, it is clear that the two substances cannot be the same (331), and Heller (331) has provided evidence which he considers to establish the fact that the Brunn principle is not identical with any of the recognized active substances in posterior lobe extracts. Nevertheless it preferentially accompanies the oxytocic principle when fractions containing this are separated from those containing the pressor substance, so that oxytocic pituitary fractions are most active in inducing the Brunn reaction in frogs. Boyd & Whyte (333) have demonstrated that oxytocic fractions are also more effective than pressor extracts in inducing the retention, by frogs kept out of water, of normal body water and of experimentally-administered water, although it is generally agreed that in mammals pressor fractions are the more effectively antidiuretic. Boyd & Garand (334) subsequently determined the influence of postpituitary extracts on the retention, by the rat, of administered water, the retention being measured over a period of five hours, so that the effect of transient antidiuretic effects would be suppressed. In these experiments with the rat, unlike those with the frog (see 335), the pressor fraction was at least ten times as effective as the

oxytocic preparation in retaining body water, the distribution, between the two fractions, of the active principle concerned being similar to that of the antidiuretic substance (334) and opposite to that of the Brunn principle. The suggestion (331, 332) that an essential difference exists between the mammal and other classes of vertebrate with respect to hormonal control of water balance thus receives support. The Brunn effect is diminished equally by total hypophysectomy of the frog, by removal of the anterior lobe only of the hypophysis, or by removal of the neural and intermediate lobes (336). The effect is also diminished by various lesions in the base of the third ventricle, a wide lesion in this position resulting in a reduction similar to that following hypophysectomy (336). At present however, little is known about the mechanism of action of the posterior pituitary principle responsible for the Brunn reaction, and investigations of the influence of posterior pituitary extract on the permeability of skin may throw light not only on this problem, but also on other questions relating to the physiology of the posterior lobe of the pituitary gland.

The antidiuretic activity of posterior pituitary extracts is unchanged in rats lacking the neurohypophysis (337). If the whole pituitary gland is extirpated, or only the anterior lobe removed, water diuresis is so greatly decreased that the animal is not suitable for the estimation of antidiuretic activity of pituitary extracts (337) and no satisfactory conclusion can be drawn. Shannon (338) has investigated the effect of variations in the state of hydration on water excretion in dogs with experimental diabetes insipidus. The oliguria produced by dehydration, and the enhancement of polyuria which results from the ingestion of saline, are both explicable on the basis of the view that the deficiencies in renal function caused by an inadequate supply of the antidiuretic hormone are an increased capacity for the reabsorption proximately, and a diminution in the active reabsorption of water distally in the tubules (338). As the results of experiments involving the administration of posterior lobe extract by constant intravenous infusion, Shannon (339) has estimated that the normal dog, weighing 10 to 15 kg., liberates 0.001 to 0.005 units of antidiuretic hormone each hour.

Winer (340) has reviewed the literature with respect to renal function in human diabetes insipidus, and has described investigations on seven cases of his own. The fall in urine volume which followed the administration of posterior pituitary extract was

accompanied by a sharp drop in the glomerular filtration rate and in the renal plasma flow, with a rise in the filtration fraction. The acute effect, which subsided in fifteen to twenty minutes, was believed to be due to a predominant constriction of the efferent arterioles.

Treatment of diabetes insipidus with slowly acting pituitary preparations has generally been successful, pitressin tannate in oil being widely used (341, 342).

Posterior pituitary gland and melanophore control.—Waring (343) has reviewed the subject of the coordination of vertebrate melanophore responses, and concludes that although other mechanisms may sometimes be concerned, the coordination of melanophore responses in elasmobranchs and amphibia is by means of pituitary hormones which circulate in the blood. In different genera of teleosts a direct nervous control of melanophores has been superimposed to a varying degree on the more archaic humoral mechanism. In an examination of the time relations of the pituitary color response in dogfish, Waring, Landgrebe & Bruce (344) adduce evidence confirming the two hormone hypothesis.

In *Fundulus* Fries (345) finds that the melanophore response, to black or white background is not affected by hypophysectomy, but that the xanthophore response to a yellow background is decreased. Some success has been claimed in the treatment of vitiligo with melanotropic pituitary extracts (346).

The implication of the melanophore factor ("B") in the control of carbohydrate metabolism is not borne out by the results of Waring, Landgrebe & Reid (347), who have obtained highly active preparations of melanophore-expanding substance which exert no hyperglycaemic or anti-insulin effect. In rabbits, the hyperglycaemia evoked by the subcutaneous injection of 0.1 mg. of epinephrine was largely inhibited by the subcutaneous administration of potent melanophore-expanding preparations containing only a trace of pressor substance, but there was no evidence that this inhibition was due to the hormone itself. Normal rabbit liver contains a melanophore excitant which, at present, is indistinguishable from the pituitary melanophore-expanding (B) hormone, but the blood or urine of normal rabbits contains no detectable amount (347).

Miscellaneous observations on the function of the posterior pituitary lobe.—The question of the influence of posterior pituitary extract on milk production has been reinvestigated by Knodt &

Petersen (348) who gave daily injections of an oxytocic fraction to cows after milking, and removed the milk which thus became available. An increase in milk yield and in milk fat production was followed by a decline after a fourteen day period of injection.

Anterior lobe adrenocorticotrophic preparations are usually contaminated with posterior lobe principles (268, 349) and the results of experiments with such preparations, together with those of further investigations on the action of pressor post pituitary extracts, have shown that daily treatment with pressor fractions can depress testis growth in rats, and injure the tubular epithelium of that organ (349).

THE INFLUENCE OF SEX HORMONES ON METABOLISM

General investigations on this subject have recently been reviewed by Kenyon (350).

The influence of sex hormone on carbohydrate metabolism.—Both Long (192, 351) and Janes (352), with their respective co-workers, have concluded that the action of diethylstilbestrol, and probably also that of other estrogens, in increasing the carbohydrate levels of fasting rats is mediated both by the anterior lobe of the hypophysis and by the cortex of the adrenal glands. The increase in glycogen stores would thus be directly effected by adrenal cortical hormones, the release of which had been determined by an enhancement of the rate of secretion of anterior pituitary adrenocorticotrophic substance, the latter being effected by the action of the estrogen on the anterior pituitary lobe. In keeping with this there is histological evidence that estrogens stimulate the secretory activity of the anterior lobe of the pituitary gland (353, 354, 355), and of the adrenal cortex (356). On the other hand, Ingle (357) has presented evidence which clearly indicates that diethylstilbestrol exerts some effect upon carbohydrate metabolism which is not mediated by the adrenal cortex. The spontaneous glycosuria of partially depancreatized rats disappeared when these animals were adrenalectomized and maintained by treatment with desoxycorticosterone, but was reintroduced by the daily administration of 0.1 mg. diethylstilbestrol. Other partially depancreatized rats, which were not spontaneously glycosuric, became diabetic during the daily administration of 0.1 mg. of diethylstilbestrol. When these animals were adrenalectomized and maintained by the daily injection of adrenal-cortical extract glycosuria developed only when diethylstilbestrol was administered. However, the dia-

betogenic effect of stilbestrol was either slight or absent when these same rats were maintained by treatment with desoxycorticosterone, or by being allowed to drink a solution of 0.9 per cent sodium chloride. Ingle (357) suggests that the failure of diethylstilbestrol to manifest its full diabetogenic effect in the absence of the adrenal cortical hormones may be due in part to the lowering of the carbohydrate stores of the body, and to the high rate of glucose oxidation, during adrenal insufficiency. The effects of pancreatectomy and of anterior pituitary extracts on carbohydrate metabolism are diminished in adrenalectomized animals, and in each case are restored by treatment with adrenal-cortical extract, but the results of such experiments do not demonstrate that these effects are entirely mediated by the hormones of the adrenal cortex. A similar state of affairs may well exist with respect to the influence of estrogens not only on carbohydrate metabolism in general, but also in bringing about a rise in the insulin content of the pancreas. The latter effect, like that on glycogen storage, is abolished in the rat by removal of the pituitary gland (358). Recently Griffiths (359) has shown that α -methylstilbene, which is known to possess only very feeble estrogenic activity, induces a significant increase in pancreatic insulin content when administered to normal rabbits. Unlike hexestrol, this substance does not produce testicular atrophy (359). The action of estrogens in causing atrophy of the gonads is probably mediated by the pituitary gland and it is of particular interest that a substance free from an obvious stigma of such an effect should be capable of bringing about a striking increase in the insulin content of the pancreas of the normal animal. The fact that diethylstilbestrol therapy can provide some protection for adrenalectomized rats against the lethal effects of low barometric pressure provides another instance of its extra-adrenal influence on metabolism (360).

Ganem (361) has reported that estrogen treatment diminished the intensity of the symptoms of diabetes mellitus in one-half of the eighteen female patients he treated thus, the results being similar with pre- or postmenopausal diabetes. This effect was considered to be mediated by the anterior pituitary gland. McCullagh (362) finds that some patients show a diminution in sugar tolerance as the result of continued treatment with methyltestosterone. In the majority of instances this diminution in sugar tolerance was accompanied by an increase in basal meta-

bolic rate. The liver glycogen stores of patients (estimated by Mirsky's phlorhizin method) and of rabbits were reduced by treatment with methyltestosterone. Whether or not these effects on carbohydrate metabolism are dependent on the presence of the anterior pituitary lobe and of the adrenal cortex is not certain, but it may be noted that treatment with testosterone propionate increases the number and size of the acidophil cells in the rat hypophysis, while the basophil cells are found to be reduced in size and to present more vacuolated and degranulated forms (363).

The influence of sex hormones on nitrogen retention and growth.—

Androgens may now be said to have achieved a definite clinical status as growth-promoting agents. The stimulating influence of androgen therapy on growth and nitrogen therapy in human beings has recently been confirmed in adult males (364, cf. however, 365), children (366, 367), eunuchoids (368), aged men (369), in a man and a woman with Addison's disease (370) and in four patients with Simmond's disease (293). The patients with Addison's disease were maintained in good condition by treatment with salt and desoxycorticosterone acetate. When 25 mg. of testosterone propionate were injected intramuscularly each day the characteristic metabolic effects of androgen therapy were observed, including diminution in urinary nitrogen, inorganic phosphorus, sulfate, sodium, and potassium, together with a gain in body weight. The basal metabolic rate, fasting respiratory quotient, and concentration of serum electrolytes were all unaltered within the time of the investigation. No reason was thus adduced for supposing that the adrenal cortex is a necessary intermediary in the metabolic response to the injection of testosterone in man (370).

In rats, the diminution in urea excretion which followed the experimental administration of testosterone propionate was associated with an increase in the arginase activity of the tissues of the liver, kidney, and intestine (371). This is the opposite of what might be expected on the basis of the results discussed on page 446 above, according to which liver arginase activity was diminished by processes which decreased the urinary excretion of nitrogen, and enhanced by agents which led to a rise in the urinary elimination of nitrogenous products.

Androgen treatment either increases the metabolic rate in human beings (360, 361) or leaves it largely unaffected (365, 368, 369, 370). It is unaltered in androgen-treated normal or castrated rats (372), although a rise may follow the administration of

methyltestosterone to thyroidectomized castrated rats (372). On the other hand the prolonged administration of diethylstilbestrol to normal male or female rats, which exerts a depressing action on the growth rate, exerts a slight and definite, though sometimes delayed, stimulating action of heat production (373). In contrast to this result with rats, Kenyon *et al.* (368) found that the daily intramuscular administration of 5 mg. of estradiol benzoate to two eunuchoids, one hypogonad woman, and one normal woman, resulted in no alteration in basal heat production but induced a reduction in the urinary excretion of nitrogen, inorganic phosphorus, and sodium. Urinary potassium was elevated in the normal woman but unaffected in the other cases. These results are similar to those obtained with androgens, and demonstrate that several of the metabolic effects of testosterone propionate are shared by estradiol benzonate if the latter is given in appropriate amounts (368).

The daily administration of 50 mg. of methyltestosterone to four normal young men for three to four weeks did not significantly alter their muscular power as measured by the strength of their grip (365) nor did it obviously influence their reaction to a short period of intense exercise. No significant change in the basal metabolic rate or nitrogen output was associated with this treatment.

The findings of different investigators with respect to the influence of androgen therapy on creatine excretion are not entirely concordant. Kenyon *et al.* (367) found that in a thirteen-year-old boy the daily administration of 5 mg. of testosterone propionate reduced urinary creatine excretions, while in eunuchoids, in which creatinuria was sustained at high levels by the ingestion of creatine, the excretion of this substance was reduced by the daily intramuscular injection of 5 mg. of testosterone propionate. The intramuscular administration of 25 mg. testosterone propionate to two cases of controlled Addison's disease (370) also reduced the excretion of creatine. Duckworth (374), on the other hand, finds that the excretion of creatine (and of creatinine) by immature males is unaffected by androgen administration, while two other groups of workers (365, 375) found that the daily administration of 50 mg. of methyl testosterone to normal young men was associated with a gradual increase in creatine excretion until it reached relatively high levels. This was accompanied by a small increase in blood creatine content, though creatinine levels in blood and urine were

unchanged (365). The creatinuria, which subsided after cessation of treatment, was not the concomitant of any evident thyroid stimulation, nor was it associated with any obvious change in muscular carbohydrate metabolism (365). Differences between the subjects, general conditions of experimentation, identity of the androgen used, and in the dose given, may all be concerned in the differences in the conclusions with respect to the influence of androgen treatment on creatine metabolism, and the results of further work on this question will be awaited with interest. It should be mentioned that Kenyon *et al.* (368) found no influence of estradiol benzoate therapy on the creatine excretion of eunuchoids who maintained a high level of creatinuria by ingestion of creatine, this result being in contrast to that obtained in similar experiments with androgen therapy (368). On the other hand, in a girl with the adrenogenital syndrome who exhibited none of the metabolic effects of estradiol benzoate therapy found in other cases, creatine excretion was increased as the result of estrogen administration (368).

As might be expected on theoretical grounds, the influence on metabolism of treatment with chorionic gonadotropin is in males similar to that of the administration of androgens (366, 367). In a boy the metabolic influence of 750 to 1500 I.U. of chorionic gonadotropin was, in some respects, more powerful than that of 5 mg. of testosterone propionate (367). In neither case was the daily injection of these amounts of the two materials accompanied by any change in the urinary excretion of androgens, estrogens, or 17-ketosteroids (367).

Miscellaneous experiments regarding the influence of sex hormones on metabolism.—The influence of estrogens in inducing lipemia in birds has been confirmed in experiments with ducks (376). In the cock the plasma phospholipid level may equal that of the liver, under the influence of treatment with diethylstilbestrol (377), but the normal level is reached again five days after the cessation of treatment. In the rat prolonged daily administration of 30 μ g. of estradiol benzoate to animals receiving a diet rich in fat but devoid of essential fatty acids resulted in an increased storage of fat in the storage of fat in the body (378).

The action of estrogen in bringing about hyperossification of the proximal subepiphyseal zone of the tibia in normal rats is not seen in hypophysectomized animals (379). In the dog prolonged estrogen treatment inhibits skeletal growth but does not produce

osteosclerosis, as it does in some other species (380). Improvement has been claimed in three out of four cases of hyperthyroidism treated by the administration of estrogen (381). It is to be presumed that such an action of estrogens may be mediated by depression of secretion of pituitary thyrotropin. In normal rats administration of diethylstilbestrol induces a rise in blood pressure, but in hypophysectomized animals a fall below the control value is obtained (382).

Treatment with testosterone propionate may induce an increase in kidney size (383), with improved functional performance, both in the dog and man (383, 384). Hamilton has reviewed the relevant literature, and his own experimental observations (385), and concludes that male hormone stimulation is prerequisite and an incitant to the development of common baldness in man.

MISCELLANEOUS

Two reviews, together with fresh observations regarding pinealoma, have recently agreed in concluding that there is at present no good evidence for the concept that the pineal body is an endocrine gland (386, 387).

Harper & Raper (388) have prepared, from the tissue of the small intestine, a substance which on intravenous injection into anaesthetized cats causes an increased secretion of enzymes by the pancreas, without affecting the volume of juice secreted. This substance, which can be separated from secretin and which has no hypoglycaemic action, is named "pancreozymin." Preparations of pancreozymin do not owe their action to vasodilator substances (388).

Foster (389) has recently reviewed cytological criteria of mammalian endocrine activity, while Benda (390) has discussed the endocrine aspects of mongolism. On the basis of autopsy material from thirty-eight cases he concludes that the developmental disorder of mongolism after birth is of pituitary origin, the hypofunction of thyroid, adrenals, and gonads being secondary.

Farmer (391) has reviewed the literature and added clinical observations of his own with respect to the role of endocrines in anaphylaxis and allergy. Agduhr (392) has discussed the role of hormones in the development of resistance to the action of noxious agents, and has emphasized the importance of the sex hormones in this connection. The account of the discussion at the Cold Spring Harbor Symposium devoted to the relation of hormones to de-

velopment (393) covers questions relating to growth and development in unicellular organisms, plants, insects, lower vertebrates, and birds, as well as problems relating to higher vertebrate life. Loeb (394) has discussed the relation of hormones to the process of ageing, while Korenchevsky (395, 396) has considered endocrine problems in relation to the influence of war time conditions on the process of ageing. Silberberg & Silberberg (397) have reviewed the influence of endocrine secretions on age changes in the epiphyseal and articular cartilages of mice, rats, and guinea pigs. Recent discussion on hormonal influences in diabetes mellitus will be found in articles by Long (398) and by Joslin (399).

Among books which have been published during the year should be mentioned a monograph from Russia concerned with the role of the pituitary gland in effects of painful stimuli, and in the activity of the nervous system (401).

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REPRODUCTION AND ITS ENDOCRINE CONTROL

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This review deals only with certain aspects of the normal reproductive processes and their endocrinological control. It is mainly restricted to mammals, and clinical reports are not included except where they are of general biological interest. With the present limitations of space it is impossible to cover in a coherent way the whole field indicated by the title, and attention has been concentrated on three subjects which are being intensively investigated or have been little emphasized in recent reviews, i.e., the normal reproductive cycle, the physiology of the ovum and spermatozoon, and the endocrine control of the mammary gland and lactation. Two contemporary reviews by the present author deal with the effects of estrogens and androgens on birds (1) and with the relationship between the adrenal cortex and the gonads (2). The intermediate metabolism of the sex hormones has also been dealt with recently (3).

The literature dealt with is mainly that which appeared in 1942 and the early part of 1943. Mention of papers dated earlier than 1942 has been made only where necessary for the discussion of recent work. Overlapping with the articles which appeared in the 1943 volume (4, 5) has been avoided so far as possible. Owing to war conditions the inevitable difficulties of reviewing current work are intensified because of the lack of access to many journals and of the general restriction of scientific intercourse, and no doubt much material, particularly European, has been missed.

THE SEXUAL CYCLE IN MAMMALS

A considerable amount of literature continues to appear on the normal features of the reproductive cycle in lower mammals, and on modifications of it not involving operative or therapeutic procedures. This work falls roughly into three categories; (a) amplification of our already detailed knowledge of the sexual cycle in laboratory animals, (b) study, mainly in its practical aspects, of the cycle in domestic animals, and (c) extension of our knowl-

edge of the reproductive cycle in wild animals and their adaptation to laboratory or controlled conditions. The menstrual cycle of the primates, about which little new information has become available in the last year or two, will not be considered in the present review.

Laboratory animals.—In the ovary of the mouse mitoses in the germinal epithelium are least frequent during diestrus, increase just before estrus, and reach a sudden high level in the short post-ovulation period. In the Graafian follicle itself mitosis is most common near the oocyte and antrum, and least common near the theca interna. In the young corpus luteum, mitosis is first most common near the extruded liquor folliculi and then near the tertiary liquor. It appears, therefore, that mitosis may be stimulated by the high concentration of estrogen known to occur in the liquor folliculi (6). The transport of ova in mice and rats (7, 8) can be studied by direct observation of the transilluminated tube. In both species, transport at the ovarian end is mainly effected by ciliary action, but lower down peristalsis is involved.

In the rat the growth of the ovary and uterus of the Sprague-Dawley albino strain, in relation to body weight, has been described (9). An investigation of cell division in the genitalia of rats during estrus, made with the aid of the colchicine technique, showed that moderate mitotic division occurs in large follicles just before ovulation, that mitosis continues in the cumulus cells surrounding the ovum in the uterine tube, that a wave of mitosis occurs in the uterine glands, and that mitosis in the basal layers of the vagina is at an ebb near the time of ovulation but increases soon after (10). A study of the effect on the rat of age at first breeding (11) shows that breeding late reduces the reproductive capacity of the female by increasing the interval between litters and reducing litter size; better results are obtained by starting to breed at puberty, but the maximum reproductivity is found when a short period is allowed to elapse after puberty before producing and raising young is begun. The average body weight at first estrus was found to be 98 gm. (12). There are definite changes in the structure of the ovaries in old female rats, including failure of ovulation and formation of wheel cells and cystic follicles (13, 14). At estrus the total blood leucocyte count shows a marked leucopenia (15). Parturition in the rat is most common between 12 noon and 6 p.m. There is considerable variation in the time taken to deliver the whole litter, but the interval between the birth of individual young

decreases as litter size increases. The average time between the end of parturition and the beginning of the postpartum estrus was about eighteen hours (16). Young rats left permanently in the light came into puberty a little earlier than those left under normal conditions, and much earlier than those kept permanently in the dark (17), though both treatments seem to decrease the size of the ovary and the number of corpora lutea (18). Mice left in darkness during the day and exposed to sixteen to seventeen hours' illumination at night showed accelerated estrus and increased pairing during the winter; daytime mating was induced (19). A neurophysiological stimulus in the form of sound from an air blast administered to rats for five minutes daily for five days a week increased the pregnancy rate as compared with controls, but depressed maternal behavior (20).

In the guinea pig, testis weight (Y) increases in relation to body weight (X) according to the formula $Y = 0.00129 X^{2.319}$ and ovary weight (Y) according to the formula $Y = 0.637 X^{0.762}$ (21). The accessory reproductive glands of the male increase in size till a body weight of over 600 gm. is attained (22). The cells of the theca interna in this species multiply rapidly during the growth of the follicle, until shortly before estrus, when they cease to divide, increase in size, and assume a glandular appearance. They disappear rapidly after estrus (23). Cyclic changes in the cervix of the guinea pig, correlated with those in the vagina, have been described (24).

In the laboratory rabbit, coitus initiates the maturation of many more ova than will ultimately be ovulated, beginning about four hours after mating. At nine hours the ovary may contain practically all stages of maturing follicles, most of which will never ovulate (25).

Domestic animals.—A general investigation of the ovarian cycle of heifers during summer in the semiarid regions of the Union of South Africa, showed that the duration of the whole cycle was 17 to 24 days, and of estrus 8 to 14 hrs., the latter being longer in the exogenous breeds (26). Ovulation, determined by rectal palpation, was found to occur at a mean time of fifteen hours before the end of estrus (27). The pH of the vaginal fluid in cows varies from 7.0 to 8.9, and is higher during diestrus and estrus, and low during metestrus (28). The total nitrogen, dry matter, viscosity, and flow elasticity of the cervical mucus of the cow all reach a maximum at estrus, and can be used to determine the occurrence of the

condition (29). Of these criteria, flow elasticity is the clearest indication and the most easily determined, and a simple instrument, the "estroscope" designed for use in the field, facilitates a rapid diagnosis (30). In pregnancy, by contrast, the cervical mucus is characterized by plasticity, and pregnancy diagnosis based on this criterion is 95 to 96 per cent correct at four months (31).

In Welsh pony mares the duration of estrus was observed to be seven days, and of diestrus sixteen days. Ovulation occurs towards the end of estrus and always takes place from the ovulation groove. Changes in the reproductive tract are also described (32). In American light and draft mares, however, estrus was found to last about five days, and the whole cycle twenty-one days. Ovulation took place one to two days before the end of heat (33). Allowing for difference of breed and locality, the figures obtained in the two investigations are very similar.

In South Africa merino ewes the actual average length of sixty-five normal estrous periods, observed at the beginning of the breeding season, was about eight hours. The average length of nineteen diestrous periods was about sixteen days (34). In small and large varieties of Poland China pigs there is no clear-cut difference in the rate of sexual development in males or females, but there is more variability in the small breed (35). The cycle in the goat can be modified by artificial illumination early in the year (36). Teat growth in this species proceeds isometrically in the period after birth, but becomes allometric in the third or fourth month (37). A study of normal histological variation in the ovaries and reproductive tract of female dogs during the estrous cycle, pregnancy, and lactation has been made with a view to providing control material for experimental work (38). Tables have been compiled for the growth of the reproductive organs of the cat (39). Additional details, including changes in the vaginal epithelium, have been described for the estrous cycle of the ferret (40).

Wild animals.—A notable feature of recent work on the sexual cycle is the discovery that delayed implantation of the blastocyst is much less uncommon than was hitherto supposed. Originally known only in the roe deer, it was afterwards described for American and European badgers. The same phenomenon has recently been reported (41) for the American long-tailed weasel (*Mustela frenata*) in which the blastocysts are formed normally during the summer and then lie dormant till the following spring when they

become implanted, gestation being then completed in a few weeks. A similar state of affairs is seen in the short-tailed weasel (*Mustela cicognani*) and the American marten (*Martes americana*). Further information is now available. Implantation of the blastocysts in both species of weasel follows the spring moult and occurs twenty-one to twenty-eight days before parturition (42). A similar type of delayed implantation occurs (43) in the Western pine marten (*Martes caurina*), in the fisher (*Martes pennanti*) (44), and in the stoat (45, 46). As a corollary to this work the extremely interesting observation has been made that implantation and continued development of the embryo can be initiated in autumn by artificially increasing the light ration in captive martens (47). It will be of great interest to see how far this extraordinary phenomenon of delayed implantation is general throughout the *Mustelidae*, but it seems certain that it does not occur in the ferret. The American marten, like the ferret, has a marked vulval swelling at estrus (48).

The sexual processes of *Elephantulus myurus jamesoni*, the elephant shrew of South Africa, have several remarkable features, notably the occurrence of a menstruation-like bleeding from a polypoid outgrowth of the endometrium at the end of the luteal phase (49). Anestrus lasts from May to July, the female being polyestrous during the breeding season (49). At ovulation an average of some sixty eggs are produced by each ovary, most or all of which are fertilised. Only one from each side, however, becomes implanted, the rest degenerating owing to the restriction of space in the uterus suitable for implantation (50). On ovulation the shell of the follicle is everted, and the corpus luteum forms as a fungiform appendix to the ovary (51). It is usually possible to recognise two generations of corpora lutea in the nonpregnant animal (52). The embryo is implanted at the four-cell stage and the endometrial reactions have been fully described (53). These may give rise to spontaneous deciduomata in the absence of pregnancy (54). Abortion may occur from the embryo chamber before implantation (55). The sequence of events in *Elephantulus* is thought to throw light on the integration of the primate menstrual cycle (56).

A study has been made of the histophysiology of the reproductive organs and processes in several species of African bat. In one species (*Nycteris luteola*), all the lactating females were pregnant,

indicating the presence of a post-partum estrus, an unusual feature for a bat (57).

In the silver fox, *Vulpes fulva*, ovulation takes place late on the first day or early on the second day of estrus, and fertilisation occurs when the eggs are in the middle portion of the uterine tube. The formation of the corpus luteum is facilitated by extensive folding of the follicular granulosa even before ovulation (58). The testes are in full spermatogenesis during the breeding season, which extends from the end of January to late in March. The early stages of spermatogenesis are seen in December. During April activity wanes. The diploid number of chromosomes is thirty-two; the sex chromosome complex in the male consists of a small Y and a larger X (59). In the Scottish wild cat (*Felis silvestris grampia*) estrus occurs early in March, and a litter is born early in May. At the end of May a second estrus occurs. In rare instances, another estrus occurs in the late autumn, the litter being born in what would otherwise be the anestrus periods which last over the winter into February. There is no seasonal variation in sexual activity in the male (60).

The Maryland musk rat has only a short anestrus period. Spermatogenesis begins in December and ovulation occurs in February. Gonadal activity terminates in both sexes at the end of October (61). In England, the musk rat mates from mid-February onwards; the first litters appear during April, and the last in August. There is a post-partum estrus, but it is doubtful if there are more than two litters a year. The average number of uterine embryos is seven (62). In the water vole (*Arvicola amphibius*), studied in England, the breeding season lasts from the end of March to mid-September. The cycle and associated changes is very similar to that of the rat (63). In voles (*Microtus agrestis*), undergoing adaptation to laboratory conditions, the prenatal mortality determined by palpation was found to be 21 per cent; 14 per cent of the young born alive died before reaching 14 days old. The sex ratio at this time was 50.89 ± 2.22 per cent males (64).

Another recently described rodent (65), the multimammate mouse of Sierra Leone (*Mastomys erythroleucus*), breeds all the year round, but some females are in temporary anestrus at all times of the year except October and November when the largest number of pregnant females is obtained. The cycle is similar to

that of the rat. The female is remarkable in having a well-developed prostate gland (66).

The breeding season in the cotton-tail rabbit (*Silvilagus floridanus*) lasts from mid-March to mid-August, as determined by the presence of enlarged uteri, ovulation, and spermatogenesis (67). The last litters appear early in September. Lactating females can become pregnant, and the average litter size is 4.4 (68). Attempts to induce winter breeding in captive specimens by artificial illumination were unsuccessful, though pseudopregnancy occurred (69). A careful study has been made of intra-uterine mortality in the wild rabbit (70), with the surprising conclusion that about one-half of all litters are lost before the twentieth day of gestation, mainly on the eleventh and twelfth days. In the European hare there have long been rumours of the occurrence of superfoetation; further evidence has now appeared of mating during pregnancy in this species and of the presence of developing embryos in a doe which had just produced a litter (71). In the white tailed deer (*Odocoileus virginianus*) pregnancy is common from December to June, and the fawns are born in May and June (72). Hedgehogs have not yet been bred in laboratory cages, but they can be bred and reared successfully in open pens (73).

A series of new records of the incidence of the breeding season in mammals transferred to a new latitude provides several instances of retention as well as of change of the breeding season (74).

THE BIOLOGY OF OVUM AND SPERMATOZOON

Parthenogenesis.—In the rat and mouse tubal eggs can readily be examined (8, 75) by transilluminating the tube. In most mammals tubal eggs are easily washed out and examined *in vitro*, as in the golden hamster (76). If desired, very large numbers of eggs can be obtained after superovulation induced by injection of gonadotrophins in the rabbit (77, 78) and in the rat (75). Formation of the second polar body in rabbit eggs, normally seen only after fertilisation, can be induced by exposure *in vitro* to hypertonic solutions or slightly raised temperature (79) and to cooling (80). Exposure to rat spermatozoa may result in activation; exposure to spermatozoa of ferret, guinea pig, bull, ram, stallion, and man rarely does so (77). Eggs activated *in vitro* may undergo segmentation as haploids, diploids, or tetraploids, and can be transplanted into other animals at an appropriate stage of the cycle. Such

procedure has been reported to lead, in a very small percentage of experiments, to the production of parthenogenetic young which are all female, but otherwise normal (77, 81). A refinement of the method is to apply the cooling process to the tubal egg *in situ* (80, 82) from which treatment one parthenogenetic litter is reported to have been produced.

In the course of the researches on rabbits it was recorded that their spermatozoa might be so damaged by exposure to ultraviolet rays as to be able to penetrate the egg but unable to effect syngamy. Eggs thus treated might undergo cleavage (79). A series of extremely interesting experiments on frogs, reminiscent of the classic work of Hertwig, has been reported (83). Exposure of frog spermatozoa to doses of x-rays between 15r and 10,000r caused a progressive increase in embryonic mortality; at the higher dose only 1.6 per cent of the embryos hatched. With larger doses, however, there was an increase in the proportion of viable embryos, a 90.5 per cent hatch being obtained with 50,000r. These embryos were morphologically uniform and very similar to haploids produced by other means. Exposure to the higher doses did not affect the motility of the sperm and it was concluded that they were able to penetrate the egg but unable to effect syngamy, with the result that parthenogenesis was initiated. Confirmation of this conclusion was obtained by beautiful experiments on the fertilisation of leopard frog eggs with bull frog sperm. The cross is a lethal one, and when the spermatozoa are untreated the embryos never proceed beyond the gastrula stage. When, however, the bull frog spermatozoa are subjected to a large dose of x-rays (60,000r) 80 per cent of the embryos hatch and develop with all the characteristics of haploid leopard frog tadpoles (84). This experiment constitutes a complete demonstration of the dual function of the spermatozoa at fertilization, activation of the egg and syngamy.

With mammals, exposure of the epididymal sperm to small doses of x-rays by irradiation of the whole animal leads to a similar deleterious effect on the embryos resulting from matings in the period before the male goes sterile. In rats, exposure of the male to 1,000r reduces litter size at birth to about one-third (85). Irradiation of mice with neutrons produces the same type of effect (86). Semi-sterility of this type, due to interchange of segments between nonhomologous chromosomes, is inherited (87) and can

be analysed by cytological methods (88). Massive dosage of x-rays can be applied to mammalian sperm by exposure of the semen *in vitro*, but attempts to produce the Hertwig effect on rabbits artificially inseminated with such semen were not successful (89).

Longevity of the ovum and spermatozoon in the reproductive tract.—The longevity of the spermatozoon in the epididymis, which has been examined in great detail in several species, was found in the rabbit to be eight days as tested by the occurrence of fertile matings, or fourteen days if motility was used as a criterion. Motile but nonfertile sperm did not reach the uterine tube after mating or survive till ovulation time (90). The long survival of the spermatozoa in the epididymis and vas deferens is probably associated with their immotility, which is often ascribed to the high local tension of carbon dioxide. Measurements, however, show that the carbon dioxide tension in these organs in rats is less than that required to immobilise spermatozoa *in vitro*, and that the minimum effective tension rapidly becomes toxic (91). It is concluded that some factor other than carbon dioxide tension is responsible for the inactivation of the spermatozoa in the male reproductive tract. The life of the spermatozoon in the female tract is short in nearly all species which have been examined. In the mouse, following artificial insemination, spermatozoa reach the uterine tube in $1\frac{1}{2}$ hrs., where they retain their fertilizing power for about 6 hrs., and their motility for $13\frac{1}{2}$ hrs. (92). In the guinea pig, spermatozoa introduced by artificial insemination before estrus retain their fertilizing power for twenty-two hours. No effect on the percentage of successful inseminations on litter size, or on the condition of the young was observed up to seventeen hours, but when the prematurity of insemination was between seventeen and twenty-two hours, the percentage successes decreased, though again no effect was noticed on development or gestation (93). In the rat, the maximum duration of fertilizing capacity of spermatozoa introduced into the female tract by artificial insemination was fourteen hours. The percentage of fertile inseminations declined when insemination was made ten hours or more before ovulation. This reduction in fertility, however, was not associated with developmental abnormalities in the young, or with an abnormal sex ratio at birth (94). Such lack of developmental effect of senility of the sperm is in marked contrast to the results of ageing of the ovum in the reciprocal experiment.

In rats inseminated at various times up to twenty hours after ovulation it was found that as the interval is prolonged there is a progressive decrease in the number of animals which become pregnant, in the percentage of those becoming pregnant which go to full term, and in litter size, and an increase in the number of abnormal pregnancies which are terminated by abortion or reabsorption. When the age of the ovum at fertilization exceeds ten hours no normal young are to be expected (95). This result confirms the general conclusion that the life of the ovum after ovulation is strictly limited.

The horse spermatozoon has a comparatively long survival period in the female tract. Insemination of mares four and six days before ovulation led to pregnancy. Two inseminations at seven days before were unsuccessful (96). By contrast, inseminations two to twenty-four hours after ovulation were all sterile, presumably because of death of the ovum. In ewes served normally by a ram, the spermatozoa reach the upper part of the uterine tube within twenty minutes. The speed of travel, which is unaffected by the stage of estrus, is thus about 4 cm. per min. (97).

Analogous investigations have also been made after natural and artificial insemination of women. Spermatozoa were found to be motile for $2\frac{1}{2}$ hrs. in the vagina, up to 48 hrs. in the cervix, and up to 24 hrs. in the uterus. They reached the uterus three minutes after coitus (98). Other figures for survival of human sperm after coitus are 25 to 60 mins. in the vagina, 40 to 48 hrs. in the cervix, and up to 25 hrs. in the uterus (99); the maximum was 37 hrs. in the vagina in 2,500 examinations, and three days in the cervix in 20 per cent of cases (100). The duration of intracervical survival of human spermatozoa is not greatly influenced by the stage of the menstrual cycle, and is not closely correlated with the *in vitro* motility of the sperm (101). However, it is clear that intracervical survival cannot necessarily be considered as a criterion of fertilizing power.

The bat has always been of especial interest in considering the longevity of spermatozoa in the female reproductive tract. The older view that in many species the eggs liberated in spring are fertilized by sperm stored in the uterus or vagina since the autumn matings was disturbed by the more recent observation that matings may take place during active periods in hibernation and also in spring. The isolation of captive females in artificial hibernation

has now shown definitely, however, that in *Eptesicus fuscus fuscus* spermatozoa can retain their fertilizing power in the female tract for ninety days (102) and their motility for 150 days (103). In *Myotis l. lucifugus* spermatozoa retained their motility for 156 days (103) though the fertilizing power of these spermatozoa was not ascertained. Improvements in the technique for maintaining bats under laboratory conditions should make possible work of great interest on the physiology of their spermatozoa. In fowl, fertile eggs are laid for fifteen to twenty days after the removal of the male, a fact indicating a considerable longevity of the spermatozoa in the female tract. The later fertile eggs, however, have a low hatchability, so that the spermatozoa presumably retain their fertilizing power after deleterious changes have commenced (104). This state of affairs does not seem to have been demonstrated in mammals, but it is reminiscent of the results on ageing of the rat ovum (95).

Collection and storage of spermatozoa.—Older methods of collecting spermatozoa, such as aspiration from the vagina and squeezing from the epididymis and vas deferens, have now largely been superseded in the case of farm animals (105) and the rabbit (106) by the use of the artificial vagina, which allows the collection of uncontaminated semen repeatedly from the same animal. The technique as applied to the stallion has been fully described (107). For smaller animals, artificially produced ejaculation has certain advantages, and methods of obtaining this response are being added to. Thus, electrical stimulation, originally applied to the guinea pig, has been worked out for the rat (108), while the substance known as gravitol, originally introduced as a uterine drug, will elicit a characteristic ejaculation reflex in the guinea pig (109). In these species, however, the coagulation of the accessory secretions makes the ejaculate difficult to handle, and, where artificial insemination is intended, it is preferable to obtain spermatozoa from the epididymis (110).

Considerable attention has been paid to the question of diluents for semen, both from the point of view of increasing volume and promoting longevity. Likewise, conditions of storage have been much studied, and several new diluents have been introduced, notably the yolk-citrate and yolk-phosphate pabula noted in the *Annual Review* (4). Untreated bull semen stores well at 40°C.; lower temperatures are unsatisfactory. Dilution with

glucose solution is not advantageous, but egg yolk buffer diluent is very effective in promoting motility of spermatozoa over the first one-hundred hours, but does not increase the longevity. Insemination of semen stored more than two to three days gave a low percentage of pregnancies (111). In contrast to artificial diluents, the addition of chick embryo extract to bull semen is reported to preserve motility for up to forty-six days, as compared with six days in untreated semen (112). In other researches, however, both yolk-phosphate and yolk-citrate diluents were found to increase motility during storage up to ten days, the fertilizing capacity of the diluted semen being maintained unimpaired for four days. The optimum temperature for storing the diluted semen was 1 to 6°C. (113). Chemical treatment of the sperm *in vitro* has not yet been found to influence the sex ratio of the offspring (114), though reports, recently reviewed (115) continue to appear on the efficacy of alkali and acid vaginal douches before mating in modifying the sex ratio.

From the start of work on the storage of semen considerable attention was paid to the effect of temperature over the range of 0 to 37°C., the general conclusion being that changes of temperature within this range should be made slowly. The optimum temperature for storage depends on the degree of shock and acclimatization, but seems to vary from 1 to 10°C. (116, 117). Recently, however, experiments of extraordinary interest and potentiality have been carried out on the effect of very low temperatures. Several years ago it was shown that if frog spermatozoa are partly dehydrated in molar-sucrose and spread in a thin film, a considerable proportion can be revived after vitrification in liquid air, the optimum conditions being rapid freezing and rapid thawing (118). Human spermatozoa in undiluted semen show marked individual variations in their resistance to low temperatures, only a small percentage from certain donors being revivifiable. Temperatures of -190°C. and -269.5°C. were not, however, more deleterious than one of -79°C. Rapid freezing and thawing was obtained by the use of capillary tubes. The survival rate was proportional to the duration of freezing and was much influenced by the freshness of the semen (119). A later investigation with human sperm showed that 67 per cent of the original live spermatozoa could be revived after exposure to a temperature of -195°C. provided the semen was very fresh, used undiluted, and plunged

into the refrigerant as a foam to ensure almost instantaneous vitrification. Less than 1 per cent of rabbit spermatozoa could be revived even under the conditions found to be most favourable, immersion of a partially dehydrated smear (120). The general principle seems to be that the formation of ice crystals must be avoided by making the change from the fluid to the vitrified condition, and *vice versa*, extremely rapid. Up to date the most extensive and promising results have been obtained with fowl spermatozoa. If fowl semen, either whole or partially dehydrated, is quickly frozen at -6°C . and quickly thawed again, no adverse effect is seen on the motility or fertilizing power of the spermatozoa. If the semen is exposed to this temperature for more than a minute, however, damage ensues, and the spermatozoa are completely destroyed after ninety minutes. Quick freezing at -76°C . of the semen partially dehydrated by addition of levulose, however, was compatible with the revival of 30 per cent of the spermatozoa and under these conditions the duration of freezing did not increase the adverse effect. Semen so treated remained viable for fifty-four days (121). A later report recorded that fowl spermatozoa could be revived after fourteen months' storage at -79°C . Insemination of hens with spermatozoa kept for an hour at -79°C . resulted in the eggs being fertile but no chicks were produced because of death of the embryos in ten to fifteen hours (122). This work obviously opens up most interesting possibilities.

Artificial insemination.—The technique of artificial insemination has received growing attention over the last two decades and is now the subject of intensive research. Insemination of farm animals has, of course, been the focus of the work. The application of the technique in horses (107) and in bovines (123) has recently been summarized. The use of semen diluted with three times its volume of glucose tartrate solution is effective in horses (124). Artificial insemination of cows in Kenya led to calving in about three-quarters of the animals. The results were not affected by varying dose or dilution of semen up to four times. Sheep also gave good results, the best time for insemination being the end of estrus (125). In South Africa, artificial insemination of merino sheep gave good results, but in Karakul sheep results were not satisfactory. Semen stored more than twelve hours decreased in fertilizing power. The technique is not thought to be of much practical value in sheep other than those with extreme tail develop-

ment, which may interfere with coitus. In laboratory animals there are records of its successful use in the guinea pig (126). In this animal, as with cattle and horses, the sperm merely needs to be deposited in the vagina during estrus. Complications, however, arise in species in which the act of coitus serves not merely to introduce spermatozoa, but to initiate some chain of neurophysiological events necessary for pregnancy. In the rabbit, in which coitus causes ovulation by stimulation of the anterior pituitary body, artificial insemination must be accompanied by mating with a vasectomized buck or by administration of ovulation-producing gonadotrophin, but even so the technique is simple and highly successful. In the rat and mouse the cervical-hypophyseal-ovarian stimulation set up by coitus and resulting in the proper development of the corpora lutea necessary for implantation of the embryo, must be initiated by mechanical or electrical means. Even with this precaution it seems necessary in the rat to inseminate directly into the uterus and to occlude the vagina with an artificial vaginal plug made of cotton wool soaked in prostatic and vesicular secretion (110). It is reported that using all these refinements it is possible to obtain full fertility by artificial insemination of the rat, but the technique is obviously complex.

Artificial insemination in fowls and turkeys provides an efficient method of obtaining fertile eggs in laying batteries, of extending the usefulness of valuable males, and effecting fertilization when birds do not mate naturally. The lower part of the vasa deferentia is stimulated by massage of the ventral pelvic region, and the semen is squeezed from the genital papillae and collected in a funnel. An average ejaculate is about 1 cc. Insemination is made directly into the oviduct from a syringe (127). The use of artificial insemination in the human subject is spreading rapidly. It seems that at least 9,000 live children had been produced by the technique in the U.S.A. up to June 1940 (128). Insemination is best performed during the mid part of the cycle, when ovulation is most likely to occur; the semen is expelled from a syringe either against or into the cervix. A high percentage of effective treatments is recorded (129).

The use of artificial insemination allows one lot of semen to be distributed between several females, and it is important, therefore, to know how many spermatozoa must be introduced to ensure that an adequate number reach the uterine tube. Methods of

examining semen particularly with reference to the number (130, 131) and condition of the sperm are constantly being improved (132, 133, 134), while remarkable histological studies have been made at great magnifications by the use of the electron microscope (135). The number of spermatozoa required varies with the vigor of the specimen, the species of animal, and other factors, and, though usually well below that present in a normal ejaculate, is always relatively enormous. Some years ago it was found that, in the rabbit, litter size decreased if the number of sperm introduced fell below 3×10^6 , and that sterility supervened when the number was below 10^4 (136). In fowl a million spermatozoa must be introduced before any fertility is obtained, and full fertility requires one hundred times this number (137). In man, fertility is unusual when the sperm count falls below 20,000,000 per cc. (138). It is most improbable that such enormous numbers are required to ensure that at least one comes in contact with the egg, but another explanation has now been provided as to why very large numbers of sperm may be required in the neighborhood of the egg before even one is able to penetrate and effect syngamy. In many species, the newly-ovulated ovum retains several layers of follicular granulosa which in the absence of sperm may remain on the ovum while it passes down the upper part of the tube. So long as this granulosa is adherent, fertilization cannot take place, or does so only with difficulty. The presence of sperm in sufficient numbers causes the tissue to disintegrate and opens a way for penetration of the egg. This reaction can easily be demonstrated *in vitro* and suspensions of dead sperm and filtrates therefrom are also effective (79). The substance exuded by the spermatozoa, already thought to be an enzyme, has now been identified with hyaluronidase, the "spreading factor" of the testis, and with the biologically similar, but antigenically distinct, hyaluronidases found in snake venom, and some strains of *B. welchii*, which are equally effective *in vitro* in clearing the egg of granulosa. The reaction apparently depends on the resolution of the hyaluronic acid complex in the jelly which binds the granulosa cells together (139, 140). Clearly, a few spermatozoa could not be expected to provide adequate amounts of the enzyme, and this work therefore supplies a reasonable explanation of the need for massive inseminations and for the sterility which ensues when the sperm count falls.

Antigenic properties of spermatozoa.—It is now well established that spermatozoa administered parenterally act as antigens and evoke the formation of antibodies which are toxic to spermatozoa *in vitro*. This reaction has been the subject of much indifferent work over a long period, and it has been invoked to explain the most diverse and uncertain phenomena, including the alleged sterility of prostitutes. However, a considerable amount of accurate experimental work has been carried out of which only the most recent is referred to here, and a good deal is now known about specificity, cross-reactions, practical implications, and so on.

Antispermatozoal sera are most readily produced when heterologous spermatozoa are injected. Iso-immunization against spermatozoa, as with lens protein, has, however, been effected in female rabbits and rats (141). Failure to produce antisera against homologous sperm has been reported in guinea pigs (142). Spermatozoa exhibit a considerable degree of organ specificity, as shown by the fact that antispermatozoal sera do not react with serum from the same species as the spermatozoa, and antisera against sera do not react with spermatozoa from the same species as the serum. Antitestis sera, however, react with brain tissue, and *vice versa*, and antisera against alcoholic extracts of these two organs have the same properties (143). Both organs show otherwise complete organ specificity except for cross-reaction with the corpus luteum (144). Spermatozoa also have a considerable degree of species specificity and antispermatozoal sera react best with homologous spermatozoa. There is, however, considerable cross-reaction which is usually better developed in closely related species, but is not entirely excluded in distantly related species, and is in fact shown by the spermatozoa of bull and man (141). These cross-reactions are perhaps facilitated by the fact that the antigenic properties of the spermatozoon depend on the presence of several different antigens. Separation of the heads and tails of bull spermatozoa by means of the magnetostriction oscillator made it possible to demonstrate the presence of a head-specific, and of a tail-specific heat-labile antigen. A third antigen, heat stable and species specific, was found to be common to heads and tails (145).

The reaction of the spermatozoa with the antisera can be shown either by slide tests (145), in which the live spermatozoa

agglutinate in the absence of, and are killed in the presence of complement, or by the complement fixation or precipitin tests (142).

The possibility of iso-immunizing a female against the spermatazoa of her own species suggested that pregnancy might thereby be prevented, but contrary to several earlier reports of positive results, recent attempts at serological contraception have been negative. Active iso-immunization of female guinea pigs with guinea pig spermatazoa led to a positive antibody response in 60 to 77 per cent of the animals, but there was no decrease in fertility. Heterologous immunization with bull spermatazoa evoked antibodies in 100 per cent of female guinea pigs, but the cross-reaction with guinea pig spermatazoa was weak and again fertility was not affected (146). Passive immunization of female mice with antisera against spermatazoa of the mouse and rat also gave negative results (147). Similarly, pregnancy in rabbits was not prevented by active immunization against sheep, guinea pig, or rabbit spermatazoa, nor in rats by active immunization against bull, sheep, rat, or guinea pig spermatazoa, or testis tissue, or by passive immunization with antirat spermatazoa rabbit serum (142). Immunization of female rabbits against a bull spermatozoal phospholipid suspended in sheep serum failed to prevent pregnancy, but a small though most unusual percentage of the young showed hermaphroditism (148). Fowl can also be iso-immunized against spermatazoa, but here again no decline in fertility was found (149).

In the same way that immunization of the female might be expected to prevent pregnancy, immunization of the male might also be expected to lead to sterility. Positive results along these lines were reported in the earlier literature, but recent confirmation seems to be lacking. The failure of active immunization with heterologous spermatazoa to prevent pregnancy in the female or cause sterility in the male, may be due to the weakness of cross-reaction with the homologous spermatazoa, and the failure of passive immunization may be due to the fact that antibodies originating in a different species are not always acceptable to animal tissues (150, 151) but the failure of active iso-immunization is curious, especially as the antibodies have been reported in the uterine fluids (142). Failure of repeated coitus to effect immunization against pregnancy is less remarkable, since such an effect

would depend not only on the possibility of iso-immunization, but also on the absorption by the reproductive tract of antigenically unchanged spermatozoal protein. This possibility cannot, however, be overlooked, since antibodies are reported to appear in the blood serum of the rabbit when guinea pig spermatozoa are introduced into the vagina (142).

ENDOCRINOLOGICAL CONTROL OF THE MAMMARY GLAND AND LACTATION

Effect of estrogens.—The capacity of the glands of hypophysectomized animals to respond to estrogens, concerning which many conflicting reports have appeared, may be much influenced by the conditions of the experiments. Estradiol dipropionate causes growth of the end buds in hypophysectomized rats of either sex if the animals weigh less than 70 gm. at the time of operation, the treatment is begun immediately, and the glands are examined after ten to twelve days (152). The administration of estrogen and progesterone or of estrogen and desoxycorticosterone causes mammary growth in hypophysectomized male mice (153). Inunction of estradiol to the mammary primordium of the male or female opossum produces hyperplasia and precocious branching of the ducts (154). Diethylstilbestrol, like the other estrogens, promotes active growth of the mammary duct system in guinea pigs (155), and in mice, rats, rabbits, and goats (156). Some years ago it was shown that inunction of estradiol benzoate to the udder of the nonparous female goat caused development similar to that seen at a late stage of pregnancy, and that subsequent injection of prolactin led to milk secretion (157). It is now known, however, that rabbits and goats may produce milk by estrogenization alone (165). Administration of diethylstilbestrol or its dipropionate to normal or castrated male goats by inunction or implantation causes increased growth of the teats, but only very slight growth of the gland. There is no secretion of milk. Inunction of the udders of virgin female goats, however, causes, after a latent period, prolonged lactation, the first milk being colostral in nature (158). The mammary glands of virgin goats increased greatly in size following implantation of pellets of diethylstilbestrol or its acetate. In some animals histological examination showed normal, though not complete, lobular-alveolar development; in others, the growth, consisting of solid masses of cells, was not normal. An aged sterile

cow also responded. Similar treatment produced little effect in a milking goat, and in a male (159). Other methods of administering the estrogen are also effective (160). Lactation was also induced in a three year old barren goat by three injections totalling 17 mg. of stilbestrol (161). The estrogen-induced lactation in the goat may be intensified by injection of anterior pituitary extract (162).

Estrogenization of nulliparous heifers was initially not very successful in producing lactation (163), but a peak yield of 33 lbs. per day has been obtained in a barren heifer (164), and it is now evident that estrogens in adequate dosage given by injection or implantation of pellets will cause complete mammary growth and lactation in virgin cattle (165, 166). This effect of estrogens is often considered to be due to stimulation of the galactopoietic action of the anterior pituitary gland, but the fact that local application may be effective with a smaller dose than is required systemically, and that unilateral effects can be obtained by inunction (167), shows that the effect must be, at least partly, direct.

The discovery that lactation can be induced in virgin heifers by the administration of stilbestrol naturally aroused interest in the possibility of inducing lactation artificially for practical dairy purposes. Whether or not the artificial induction of lactation would ever be desirable in normal animals, it seemed a promising method of handling sterile heifers and even dry barren cows, especially during wartime when the maintenance of the milk supply is of the greatest importance and presents special difficulties. Extensive trials have been carried out in England during the last three years under the auspices of the Agricultural Research Council, and the results have been recorded. Implantation of tablets of diethylstilbestrol or hexestrol, totalling 2 gm. to 5 gm., into each of about thirty virgin heifers and dry barren cows resulted in widely different degrees of lactation. Daily yields were frequently greater than two gallons within two months of the start of treatment, while one cow showed a peak daily yield of three gallons and a year's total of 740 gallons (168). Ovarian hypoplasia and nymphomania were usually associated with treatment, and pelvic fractures were sometimes encountered. In another series of experiments on about sixty heifers and cows, tablets of diethylstilbestrol or hexestrol were implanted to give a total dosage of 0.4 gm. to 5 gm. over thirty to two hundred days. In heifers, the udders became tense in about two weeks. The yield of milk rose, not always

steadily, for forty days or more. The presence of a persistent corpus luteum, as in pregnancy, seemed to inhibit milk secretion. In the majority of heifers the yield of milk approached what might have been expected in a first lactation. Removal of the tablets sometimes caused a considerable increase in milk yield, as did a single injection of 200 mg. diethylstilbestrol in oil where the yield was abnormally low. The ovarian cycle was suppressed, but was resumed soon after cessation of treatment. Heifers previously sterile might get in calf during the induced lactation. Results with dry barren cows were much less satisfactory (169). Oral administration of diethylstilbestrol, hexestrol, or dienestrol, induced lactation in twenty-seven out of forty heifers, but the method is less economical and results in a slower onset of lactation and much lower yields (170). Similarly, implantation of tablets, made for practical convenience in manufacture with 40 per cent lactose as excipient, did not give satisfactory results (171). Attempts to simplify the process by substituting a single injection of one or more esters of diethylstilbestrol were only partially successful. Most of the esters used, dipropionate, dibutyrate, dicaproate, dicaprylate, dilaurate, dipalmitate, and dibenzoate, alone or in combination, induced lactation by a single injection, but in only two heifers out of twenty four did the yield exceed one gallon daily (172). The milk produced during such induced lactation has a normal content of fat, nonfatty solids, nitrogen, lactose, and phosphatase, when a yield of 5 lbs. daily has been attained. Earlier secretions are colostrum in type (173).

In contrast to this capacity of the estrogens to induce lactation in animals of several different species, administration during established lactation usually depresses milk yield. This has been thought to be true for the rat, but recent experiments point to the possibility that decreased growth of the young associated with estrogenization of the nursing mother is due to loss of maternal instinct and neglect of the young rather than to suppression of lactation. Effects on both male and female young indicate that a part of the injected estrogen passes into the milk (174). The delayed implantation found in pregnancy concurrent with lactation in the rat has been ascribed to an analogous loss of endogenous estrogen in the milk (175). Prolonged injection of estrogen to mice during lactation increased the size and number of the active areas of the

mammary gland, but did not prevent regression of the gland at the normal time (176). Moderate doses of diethylstilbestrol given to a cow in established lactation may cause a rise in milk solids without affecting milk yield (177, 178); larger doses may in addition cause a decline in milk yield (177). The inhibitory effect is more readily obtained in normal than in ovariectomized animals and an index is thereby obtained of the estrogen production by the normal ovary (179). Diethylstilbestrol has, however, been reported to cause a 100 per cent increase in the milk yield of an ovariectomized heifer (165).

The inhibitory effect of estrogens on lactation is well seen in women; in 134 cases lactation was effectively suppressed by oral administration of diethylstilbestrol, dienestrol, or hexestrol (180). Ethinyl estradiol, an orally active estrogen, in a daily dose of 1.5 mg. or more suppressed lactation in puerperal women. Smaller doses were ineffective (181). Diethylstilbestrol has, however, been reported to prevent the initiation of lactation in women in doses of 3 to 10 mg. daily for two to four days (182), but to be less effective when lactation has started (183). Painful engorgement of the breasts is also relieved by administration of stilbestrol, an effective dose being 5 mg. daily (184). Similar results both in suppressing lactation and in relieving painful engorgement have been described in another series of patients (185).

Effect of progesterone.—Injection into spayed female rabbits daily for four weeks of 200 I.U. estrone, together with 1 I.U. of progesterone, brought the mammary gland up to approximately the condition seen in a three weeks pregnant rabbit (186). In spayed rats, the daily injection of 15 mg. of progesterone caused some development of the lobule-alveolar system of the mammary gland, but the effect was less than that produced by 33 μ g. of estradiol benzoate (187). Dosage of progesterone up to 15 mg. daily produced no apparent effect on lactation in rats; a slight, but doubtfully significant effect was obtained with 4 mg. daily of pregnenolone (188).

Effect of androgens.—Injections of testosterone propionate into virgin rats late in estrus caused development in the mammary acini within twenty days, and resulted in lactation if the stimulus of suckling was applied. This effect, however, was thought to be dependent on the production of progesterone by the corpora

lutea which hypertrophy as a result of treatment with testosterone (189). Testosterone was found to produce thickening of the mammary ducts in hypophysectomized male rats, an observation which may explain the synergistic effect of the androgen when given with the lobular-alveolar stimulating pituitary mammo-gen (152). Testosterone propionate, administered by pellet implantation, did not cause grossly visible stimulation of the mammary glands of prepubertal rats in ten days. In pubertal and postpubertal animals, however, the glands responded (190). In the rhesus monkey, preadolescent treatment with testosterone propionate induced a secretory condition in the mammary gland epithelium, but did not promote alveolar development. Three other androgens, Δ^4 -*trans*-dehydro-androsterone, Δ^5 -*trans*-androstenediol, and *cis*-androsterone, caused the same reaction in varying degrees. (191).

The twice daily inunction of 4 mg. of testosterone propionate in ointment inhibited lactation in sixty-eight out of one hundred women, but in no instance was lactation completely suppressed (192). Testosterone propionate in a dose of 70 to 75 mg. over three days suppressed lactation in women (193), but the substance has been found to be ineffective in suppressing painful engorgement of the breasts (185). Methyl testosterone, given by mouth, in doses of three 10 mg. tablets, three times a day for three days, has the same kind of effect (194). Higher doses (250 mg. to 300 mg.) are also recommended (195). Testosterone propionate (2 mg. daily) will suppress lactation and cause premature involution of the mammary gland in rats, in spite of the continued stimulation of suckling. The high death rate among the young is not due to abolition of the maternal instinct (196).

The anterior pituitary gland and lactation.—Evidence of the essential role of the anterior pituitary gland in the normal control of lactation continues to accumulate. It has recently been reported that, while ovariectomy has no effect on the course of involution of the mammary gland in the mouse, hypophysectomy greatly accelerates the involution which follows the removal of the young in midlactation (197). Hypophysectomy of the mouse at the twelfth day of pregnancy, however, does not prevent the birth of normal young at term (198), the development of the mammary glands during the second half of pregnancy, or the ini-

tiation of lactation (199). There must, therefore, be some non-hypophyseal source of mammotrophic and lactogenic hormone in the pregnant mouse. This source is abolished by parturition, since lactation is not maintained in the hypophysectomized animal (198).

The best known of the several pituitary factors which appear to be associated with mammary development and lactation is the so-called lactogenic hormone, prolactin. This substance has now been obtained in such a form that it behaves as a homogeneous protein in electrophoretic, solubility, and diffusion tests. In this state it has an activity of 25 to 30 I.U. per mg., as compared with the 10 I.U. per mg. of the International Standard (200). The methionine and cysteine content of this substance was found to be 4.31 per cent and 3.11 per cent respectively, the two together accounting for the whole of the sulphur content (201). Purified prolactin is inactivated by more than two hundred times its weight of cysteine (202). A homogeneous crystalline protein has also been prepared from highly purified amorphous prolactin; the crystalline material has 30 to 35 I.U. per mg., a molecular weight of 32,000, and is heat stable at pH 1 to 9 (203). Partly purified prolactin is highly soluble in 99.8 per cent methyl alcohol and 95 per cent ethyl alcohol at a pH below its isoelectric point (204). A method has been outlined for its direct extraction from fresh pituitary tissue by chloroform and acid methyl alcohol, the final product having an activity of 30 I.U. per mg. (205). Other methods of obtaining preparations of prolactin with high activity (25 to 30 I.U. per mg.) have also been described (206).

The micromethod for assaying prolactin, local administration of the test substance, is not entirely specific, since damage to the superficial skin and injection of a variety of nonspecific substances leads to stimulation of cell division in the crop gland (207).

Prolactin in doses of 0.5 mg. to 2.0 mg. given daily subcutaneously to immature female rats causes lobular development of the mammary gland (208). A daily dose of 60 I.U. together with 10 I.U. of estrone causes alveolar-lobule development in hypophysectomized rats equal to that seen in the first half of normal pregnancy, and such treatment is partially effective in maintaining pregnancy after removal of the pituitary gland (209). Administered to post-partum mice the substance prolongs mammary activity

in the absence of suckling (210). That prolactin acts directly on the prepared mammary gland and not through some intermediate agency has been shown most ingeniously. Rabbits were ovariectomized and injected for four weeks with estrone and progesterone. Prolactin was then administered by injection into the ducts through the teat. Treated glands receiving 3 or 6 I.U. produced milk, though the adjacent glands, untreated, showed no response (186). Injection of prolactin causes secretory changes in transplanted tumors in nursing rats, but not in males or nonnursing females (211).

Interesting observations continue to accumulate on the effect of prolactin on reproductive processes other than lactation. Administration of prolactin does not delay, and may even slightly expedite the time of vaginal opening in young female rats (208). It appears, however, to have a definitely stimulating effect on corpora lutea, as confirmed by recent experiments showing that it prolongs the time during which deciduomata can be evoked in the lactating rat (212), and facilitates implantation of the blastocysts in rats hypophysectomized soon after mating (213, 214).

The amount of prolactin present in the anterior pituitary gland varies considerably according to the species and the physiological state of the animal, and under experimental conditions. The content during pregnancy is greater and has a higher maximum level after parturition in the mouse than in the rat, guinea pig, and rabbit (215). In the last of these species the content from the second day post-partum is much less in nonsuckling than in suckling does (216). During pseudopregnancy the amount present is about the same as in normal or pregnant rabbits (217). Adrenalectomy causes a decrease in prolactin present in the rat pituitary gland (218); injection of estrone increases it (219). Examination of the prolactin content of the pituitary of two breeds of pigeon showed that, as in mammals, the gland in the female contained more than twice as much hormone as in the male, and that the gland in one breed contained much more hormone in relation to body weight than it did in the other breed (220).

Further work has been carried out on the mammogenic duct growth and lobule-alveolar growth factors of the hypophysis. The mouse unit of the former is defined as "the total amount of tissue or extract required to produce definite signs of development in one

or more glands of 50 ± 10 per cent of ten male albino mice weighing 10g.-25g," injections being made daily for six successive days and the animals killed on the seventh day. The mouse unit of the lobule and alveolar growth factor is defined as "the total amount of material required per mouse, injected subcutaneously daily over a period of ten days, to obtain definite lobule-alveolar development in 50 ± 10 per cent of ten or more castrate nulliparous female mice weighing between 12 and 18 g.," the effectiveness of the mammogen being enhanced by the simultaneous injection of 75 I.U. of estrogen per mouse (206). The hypophyseal factor which promotes growth of the mammary lobule-alveolar system is definitely protein in nature, and is distinct from the lactogenic, thyrotropic, and gonadotropic hormones, as shown by the differential assay of a group of pituitary extracts (221). The evidence in favor of the existence in the anterior pituitary gland of a distinct fat-soluble substance causing mammary duct growth has been added to by experiments on hypophysectomized-gonadectomized male and female guinea pigs. The duct system of such animals can be made to grow by the implantation of fresh anterior pituitary gland, or by the injection of an ether-alcohol soluble extract showing no activity characteristic of the recognized pituitary hormones (222). Nevertheless, it is reported that one-half or two-thirds of the mammogen content is retained in the pituitary tissue after dehydration in three volumes of acetone (206). An extract of the dried powder made with 60 per cent alcohol contained only a small part of the mammogen.

The thyroid gland and lactation.—Thyroidectomy of normal or castrated immature male rats inhibited mammary duct growth but stimulated alveolar development. The latter effect in castrated animals was increased by treatment with testosterone or estradiol. In certain circumstances, therefore, the two steroids can exert the same effect (223). Thyroidectomy of normal or spayed young female rats stimulated the development of the lateral and end buds, but in addition it caused thickening of the ducts. Administration of thyroxine tended to prevent these changes (224). The simultaneous injection of thyroxine at an optimum dose level can potentiate the effect of estrone and progesterone in causing lobule-alveolar development (225, 226). It has also been found that thyroidectomy before conception, or during gestation, does not prevent the normal

evolution of the mammary glands to the lactating state (227). In normal but not in castrated mice, the addition of 1.5 mg. of desiccated thyroid per kg. of food causes proliferation of the mammary ducts and end buds (228). Thyroidectomy of the lactating rat has been reported to decrease but not to abolish milk secretion, as evidenced by the continued but decreased growth of young. The effect is thought to be due to an indirect effect on the hypophyseal formation of prolactin (227). In other experiments, thyroidectomy during lactation caused immediate cessation of litter growth and therefore presumably of milk secretion. Litter growth was partially maintained in such animals by the administration of parathyroid extract or by the autoplasmic grafting of thyroid tissue containing parathyroid. It is concluded that the effect of thyroidectomy is due at least in part to parathyroid deficiency (229, 230).

Oral administration of desiccated thyroid, or the injection of thyroxine to cows in declining lactation gives considerable increase in milk yield; there is also an appreciable increase in milk fat and nonfatty solids. After treatment, the quantity and quality of the milk falls to pre-injection levels, but afterwards regains the level which would have been expected at that time in the absence of treatment (231 to 235). The nature of the milk fat is unchanged (236). This effect of thyroid powder or thyroxine can be reproduced by oral administration of artificially iodinated protein. 50 gm. to 100 gm. daily of iodocasein for three days caused, in fourteen trials, a rise in milk yield which lasted three days after the cessation of treatment. Afterwards, as with the natural product, there was a drop below the pretreatment level. Similar treatment of lactating goats caused an increase in milk yield of up to 4 per cent (237). Iodocasein also increases milk fat percentage in cows and yield of butter fat (238), though this may not occur regularly (239). Iodocasein reproduces other effects of dried thyroid and thyroxine, such as increasing the basal metabolic rate of guinea pigs, and expediting the metamorphosis of tadpoles (239), and promoting growth in thyroidectomized goats (240); it is reasonably certain, therefore, that its effect in cows is exerted by virtue of its thyroid-like properties. Unspecific stimulation of the metabolism with dinitrophenol, in doses sufficient to raise respiration by 41 per cent and pulse rate by 53 per cent, has been reported to decrease the yield of both milk and butter fat (241). The economic

possibilities of the use of dried thyroid for promoting milk yield were, of course, limited by the lack of bulk supplies, and by the cost. These difficulties apply much less to artificially iodinated protein, and interesting developments may be expected.

The adrenals and lactation.—Massive doses (5 mg. or 10 mg. daily) of desoxycorticosterone produced no effect on lactation in rats as evidenced by the growth rate of the young (188). By contrast, gynecomastia has been reported in a man following the administration of 15 mg. to 20 mg. of desoxycorticosterone acetate daily for two weeks. Cortical extract did not have this effect (242). Previous reports, however, indicate that under certain conditions desoxycorticosterone acetate may depress lactation in nursing rats (243), and in guinea pigs in which the mammary gland has been stimulated with estrogen (244). Moreover, it seems that the maintenance of adrenalectomized nursing rats on desoxycorticosterone acetate does not maintain the lactation, which, in the absence of effective replacement therapy, is suppressed by the operation (243).

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PHYSIOLOGICAL PSYCHOLOGY

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The opportunity to review the subject of physiological psychology at this time is notably facilitated by the publication within the last few months of two volumes with this title. Hathaway (1) has written a rather concise text for the *Century* series, and Morgan (2), a much more elaborate one, which is really more a neurophysiology than a psychology text. The availability of these volumes, which cover the whole field up to the present time, permits the reviewers to concentrate upon certain topics that are almost too new to receive sufficient consideration in the more general works. We believe that physiological psychology has advanced enormously during the past few years owing to newly developed technics applicable to man, and to refined technics for the study of the higher nervous regulations in animals. Briefly, we propose to limit our discussion to three fields where the principles of physiological psychology are being developed most rapidly. These are (a) psychosurgery, (b) shock therapy, and (c) experimental neuroses. Even in these relatively narrow fields we are particularly fortunate in having available in monographic form some of the most important investigations of the past decade.

PSYCHOSURGERY

Psychosurgery, as Freeman & Watts (3) point out in their monograph, consists in operation upon the anatomically intact brain for the purpose of relieving mental abnormalities. We have found, following the pioneer work of Egas Moniz, that best clinical results are obtained when the white matter of both frontal lobes is incised in the plane of the coronal suture. This review does not purport to be a discussion of the clinical features, except insofar as they pertain to the subject of physiological psychology, yet since the behavior of mentally sick people is profoundly altered by operation, the results of operation will have to be dealt with in terms of behavior. There are relatively few objective measurements that are yet available for the study of the problem in any other way. Furthermore, the neurological signs following opera-

tion lie more in the field of neurophysiology and will be omitted from consideration. What we are concerned with is the functioning of the individual who is surgically deprived temporarily of the functioning of a considerable proportion of his frontal lobes, who thereby regresses to an infantile level of behavior, and who in the succeeding months "grows up" with astounding rapidity to resume an active, socially acceptable existence freed from the burden of crippling mental handicaps. On this topic, Hutton (4) states:

For the first time in history, an opportunity has been presented for the study of changes in personality produced by a relatively standardized local lesion of the brain, enabling us to investigate as never before the role of the frontal lobe in normal and abnormal mental states.

Prefrontal lobotomy is carried out preferably with the patient under local anesthesia so that his conversation can be recorded during the various steps of the operation. The response to the preliminary stages such as incising the scalp, drilling the holes, and taking the "soundings" is quite variable. Some patients are restless and apprehensive (as might be expected!), others are calm either with the tenseness of facing death (5) or with their preoccupations still dominant, or even in a catatonic state. Some are easily led to a discussion of their emotional difficulties and are not distracted by the operative procedure. This discussion can be continued with perfect cooperation after the incisions in the frontal lobe are completed on either side, or after incisions are made symmetrically in both upper halves or both lower halves of the two frontal lobes. When the third "quadrant" is sectioned there is a notable falling off in the length of the replies, in their circumstantiality, and in the display of emotion connected with them. Spontaneous observations on the part of the patient are limited to complaints of pain, and even nausea and vomiting may occur without warning. When questioned, the patient with three "quadrants" incised is found to be still in contact with his environment, and his voice still has a certain liveliness. Indeed, some patients with severe depression and retardation begin to speak more freely at this stage than before, and upon request may recite well known verses, do the 100-7 test, say their prayers, and even sing with adequate modulation and expression. When the fourth "quadrant" is sectioned, the patient usually becomes unresponsive except to urgent questions, his replies are monosyllabic, his face is expressionless, and his orientation is lost. He may even deny

that he is being operated upon. Any pre-existing nervous tension is lost, with corresponding effects upon the pulse rate and blood pressure, and the incisions are closed with the patient in a state resembling sleep. The patient is not asleep, however; when sufficiently stimulated he opens his eyes, smiles at relatives, gives his hand in greeting, and then sinks back into his former completely indifferent state.

At first we were inclined to attribute this condition to diaschisis. It seemed likely that such an extensive sectioning of neural pathways must lead to neural "shock" within the central nervous system that would throw out of action large groups of neurons. However, with further experience we have noted on a number of occasions that the flattening and disorientation did not appear until certain stab incisions were made in the depths of the quadrant sweeping incisions. In some cases it seemed as though a certain relatively small bundle of fibers was preserving the patient's contact with reality, and when this was sectioned the patient drifted off into confusion and unresponsiveness. As closely as can be judged from a number of different angulations of this particular incision, the bundle is located close to the midline at about the level of the genu of the corpus callosum. The fasciculus cinguli is in this location, but it is not yet known whether this is the critical bundle. Certainly it is not the corpus callosum, according to Akelaitis (6), since Van Wagenen has sectioned this body throughout its length without causing disorientation; nor is it the fornix, since the lobotomy incisions lie well in advance of this structure.

Most of the effects of prefrontal lobotomy have been attributed to interruption of the thalamofrontal radiation. Indeed, our pathologic studies have shown that there is little or no change in the cerebral cortex anterior to the incisions, and the cortical damage resulting from operation is trivial. Furthermore, the nucleus medialis dorsalis of the thalamus undergoes severe retrograde changes in response to lobotomy, losing most of its cells, while the other nuclei are unaltered. There is finally a quantitative relationship between the extent of transection of the radiation and the number of cells lost. Marchi preparations show that there is little degeneration of the pathways except anterior to the incisions, this fact indicating that the pathway is predominantly thalamofrontal rather than frontothalamic.

These pathologic findings are of great significance in the understanding of the changes in personality brought about by prefrontal lobotomy. Fundamentally it would appear that the frontal cortex is isolated from the thalamus and no longer receives the thalamic component except by indirect means, and conversely that whatever organized activity may be present in the frontal lobes has to find its expression by somewhat devious routes since the direct pathways are severed. No doubt these pathways are developed to some degree with the passage of time, since the patient with a lobotomy is often capable of excellent social and working adjustment, whereas the patient with a bifrontal lobectomy is permanently crippled to a greater or lesser degree according to Brickner, Ackerly, Karnosh, Hebb and Penfield and others cited by us (3a). Yet even in these patients there is resumption of a considerable degree of socially acceptable behavior. These facts indicate that a man is capable of a great number of delicate adjustments with a minimum quantity of frontal lobe. Perception, apperception, memory, language, and basic intelligence are intact. Motor and sensory functions are unaltered. The autonomic functions are even stabilized, or appear to be, since patients are no longer troubled by their perturbations.

Following the initial period (two to five days) of lethargy and disorientation after lobotomy during which the patient has to be tended like a baby, fed, watered, and changed because of incontinence, there appears a stage of serene relaxation and indolence that may last for several days. During this time there is placid acceptance of the attentions of relatives varied with playful gestures and remarks and not infrequently persistent stereotyped overactivity in a vague semidazed condition. Papers and magazines are scanned with intensity but without appreciation of content, the daily toilet is prolonged indefinitely, eating is very leisurely, and the passage of time is unnoticed. A good deal depends upon the prepsychotic personality of the patient, the duration of the psychosis, and the stereotyped nature of the complaints or the compulsions. In patients who have manifested chronic anxiety as the outstanding symptom, normality returns very rapidly; in those who have suffered from hallucinations, delusions, obsessions, hypochondriacal complaints, compulsions, and other specific and durable mental symptoms, the patterns of the reactions continue even though the emotional component has evaporated. One speaks of echo symptoms.

Once the patient returns to his home, about two weeks after lobotomy, the newly emerging personality is fairly well developed and continues its evolution for a period of many months or even years. It is not a healthy personality at first; probably the word immature best describes it. Granting that the disease symptoms have been relieved by operation, the patient manifests two outstanding traits that could be described as laziness and tactlessness. In some people indolence is outstanding, in others hastiness, explosiveness, petulance, talkativeness, laughter, and other signs of lack of self-control. These patients know that they ought to busy themselves about the house, but they procrastinate; they know they should be considerate of their relatives and dignified in the presence of strangers, but it's too much trouble. They are often buoyant and exuberant, and many times they have been likened to children by their observant relatives. Their interest span is short, they are distractible, but their good humor is almost invincible. They cannot be serious. They do not dream.

Further maturation of the personality occurs with the lapse of weeks and months. The housewife complains of forgetfulness when she is really describing distractibility and lack of correct timing of the various household maneuvers. The man makes up his mind to look for a job but he can't quite summon up the energy necessary to overcome his inertia, and the many facets of the problem of obtaining employment are too numerous for his still limited capacity for consecutive and constructive thought. If he has a job to go back to he is apt to lose it because of errors of judgment and foresight. A lawyer noted that previous to operation he had been able, following an interruption, to resume his dictation at the exact word, whereas afterwards he had to have his secretary read her notes to him before he could resume his trend of thought. Capacity for constructive thinking increases with lapse of time, and initiative also improves. Some patients even become overly energetic, seeming to lose themselves in their work, even oblivious to the state of normal fatigue. From being distractible early in their postoperative course they become quite undistractable. Naturally indolent persons, however, who previously drove themselves beyond their capacity, are apt to be satisfied with activities far short of their previous aims.

As in the case with indolence, so also tactlessness tends to disappear in the months and years following lobotomy. Patients regain more or less completely their capacity to conduct themselves

in a dignified and considerate manner particularly with strangers, although they may revert to their more immature behavior in the family surroundings. It is not that they don't know better, for many of them will confess their lapses, but they either cannot foresee the effect of their hasty words or actions, or they just don't give a damn.

It is this emotional "set" that characterizes people who have been operated upon. The outstanding feature is lack of self-consciousness in the sense that they are childlike in the expression of their attitudes. They do not take themselves seriously. They cannot be insulted; no matter what one says to them they do not take offense. They laugh easily and flare up in anger on slight nagging or frustration, but seldom weep. They enjoy the pleasures and avoid the disagreeable facts of life as much as they are allowed to. Life is enormously simplified by the relatively complete obliteration of the need for introspection. Basic intelligence is intact, planning capacity is adequate, foresight is direct, decision is abrupt, acceptance of the results is realistic, and the emotional responses are vivid though evanescent and lacking in depth. On the whole, a patient who has satisfactorily recovered from a psychosis through psychosurgery gives the impression of a pleasant and enthusiastic if somewhat immature individual whose willingness to fall in with the "set" of the other person's attitude makes him an agreeable companion. People on whom this operation has been performed are generous, steady, fairly reliable workers, friendly, and unembarrassed at being interviewed by strangers. They take things as they come.

Functions of the frontal lobes.—From the above description of the social behavior of patients who have undergone prefrontal lobotomy we are justified in assuming that the division of the thalamofrontal radiation has had a profound effect upon the emotion that is attached to the image the patient has of himself. The highly personal aspect of this attitude has only recently been realized in connection with the frontal lobes. While foresight, synthesis, planning capacity, organization of behavior, social sense, and other designations have been employed by various authors to indicate their concept of functions of the frontal lobe, these writers have tended to neglect the relationship of these functions to the individual himself. In other words it is not foresight in the general connotation, but foresight as to the specific relationship to the

individual that is impaired for a period after prefrontal lobotomy. In the later stages it is not even this foresight, but rather the emotional attitude toward the image of the self as projected into the future, that undergoes a profound reduction. Impersonal aspects of situations are handled with much greater effectiveness than personal implications. Planned activity is quite adequate as far as business affairs, games, and so on are concerned, but subtlety is lacking, the approach being direct and ingenuous. A devious campaign toward a distant goal is apparently not worth the effort.

One may say, therefore, that the prefrontal regions bring the self into relation with the self, aid in the delay and long-circuiting of reactions, make for restraint as far as the expression of emotions is concerned, and check the emotional "set" without interfering with administrative capacity once the goal is chosen. Furthermore the frontal lobes are important for insight, for subtlety, for postponing pleasure, and for projecting the individual into the future. They are essential for the elaboration of a vivid picture of the future with all its deviations, all its implications, all its difficulties and dangers, all its triumphs and disasters. The healthy individual lives largely in the future, his interests adequately balanced between himself and his environment. The operated patient "lives in a perpetual present" (7), his interests in the outside world being much more vivid than his interests in his reactions to them. The depressed individual lives in himself, with the outside world more or less shut out and the future looming black and threatening. We conclude that without the frontal lobes there could be no functional psychoses.

There is a quantitative relationship between the amount of frontal lobe disconnected from the rest of the brain and the effect in terms both of clinical result and of personality integration. We have observed that incisions placed too far anterior to the plane of the coronal suture, or at insufficient depth, result in very little alteration in the patient's emotional attitude or his overt behavior. When the plane of section is farther back but still somewhat in advance of the coronal suture, the postoperative course is characterized by euphoria, talkativeness, and exuberance. This state soon gives way to a normal appreciation of self and surroundings, and usually to a return of the former disabling mental symptoms. On the other hand, when the incisions in the frontal lobes are made

behind the optimal plane there is always a profound and prolonged depression in the individual's awareness, followed by more or less persistent vacuous euphoria and inertia.

Secondary operations are necessary in some 20 per cent of our cases. These procedures have given us the opportunity of observing how the personality of the patient is altered with successive amounts of frontal lobe tissue disconnected from the rest of the brain. Some operations are performed within a few days, others after weeks, months, or years, during which the patient may have led an independent and effective working existence followed by relapse and disability. The psychotic relapse is just as resistant to ordinary modes of treatment, or even shock therapy, as is the primary disorder. A second operation relieves most patients but some require even a third procedure. Such repeated operations greatly reduce the capacity of the patient to undertake any but the simplest adaptations, but the emotional nucleus of the psychosis can usually be eliminated. In other words, for example, when approximately 65 per cent of the frontal lobe connections are severed the patient is still disabled by preoccupation with his self-directed ideas, whereas when approximately 85 per cent of the frontal lobe connections are severed the patient is disabled by lack of sufficient capacity to organize his behavior. The relief of mental distress is accomplished but at high cost to the individual, since following a secondary operation, he loses much more constructive imagination, initiative, and self-control.

Different patients require inactivation of different amounts of frontal lobe tissue for banishment of the self-directed preoccupation. Well-integrated individuals with disabling tension states but no schizoid distortion respond to minimal interruptions, while schizophrenics, chronic obsessives, hypochondriacs, and long-term involuntaries require the placement of lesions far posterior in the prefrontal regions. This would seem to indicate that the physiological organization of the neural constituents underlying psychotic behavior extends with the passage of time and with constant repetitive thinking and behavior to adjacent portions of the frontal lobes that are ordinarily concerned with more impersonal or social organization of the behavior of the individual.

Finally, the fact that a minimal operation, in terms of frontal lobe tissue inactivated, will succeed in an early case in a state of panic, whereas a maximal operation will fail in a long-established case where the symptoms have become milder through dying out

of the emotional responses, seems further to indicate that it is the emotional component that fixes and extends the pathologic process both in terms of behavior and of its necessary anatomical substrate. Dying-out of the emotional responses in a patient is an indication that clinical improvement cannot be obtained without sacrifice of most of the remaining adaptive mechanisms that are still present. A deteriorated schizophrenic looks and acts about the same with or without his frontal lobes.

Since the publication of our monograph which contains all references to psychosurgery through 1941 there have been a number of similar reports dealing mostly with technical and clinical aspects. Strecker, Palmer & Grant (8) found that:

The outstanding clinical result was the disappearance in very large degree of destructive and dangerous clashes with the environment. Psychological testing did not reveal measurable post-operative intellectual defect. In general, emotional responses appear to have been freed, or at least rendered more flexible. Contrary to the accepted opinion concerning the inhibitory reduction and super-ego blunting in frontal lobe pathology, two of our [5] patients regained a considerable measure of inhibitory function and self-critique, and two others profited in measurable degree. There seem to be qualitative personality alterations, or, perhaps, restorations, determining social adaptabilities. In two patients former disregard of others has been replaced by manifestations of thoughtfulness, consideration and generosity. Pre-psychotic artistic capacities and inclinations and skill in games, athletic and non-athletic, have been strikingly revived in two patients and partially in one . . . In three patients, either there appeared or there was resumed the capacity to anticipate the future, visualize it usually pleasurably as in the matter of trips, cruises, theater, etc.

According to Fleming & McKissock (9): "Several of the patients have themselves stated that they have found complete 'peace of mind' after the operation and this does appear to us to be an outstanding fact about it and a very important one in patients who for years have been suffering torment." Banay (10) studied a compulsive sexual psychopath who was relieved by operation; a Rorschach test by Harrower-Erickson revealed a better integrated emotional response than was present in any other of the fifty similar but unoperated subjects.

Hutton (7), on the basis of fifty cases, concludes: "They are not incapable of taking thought for the morrow should anything stimulate them to do so, but they are quite content for the morrow to take care of itself. They live in a perpetual present that is dependent upon associative memory." In an earlier article (4) she deals at some length with psychological considerations. Drawing

upon the ideas of Bergson and of Ribot, and apparently seeking an explanation for the behavior before and after operation on the basis of motor activities controlled by the frontal lobes, she suggests that:

the maintenance of these (abnormal) ideas and images is dependent upon the maintenance of certain muscular adjustments which were necessary for their original perception. It now becomes possible to understand why the severance of certain pathways concerned with the organization of movement in the prefrontal lobe should result in such a striking change in the patient's behavior. Being no longer able to revive or recall these ideas by spontaneous adoption of the necessary movements their behavior is now controlled by ideas and images prompted directly by their environment and is therefore more appropriate to the situation.

Most of us are mainly dependent upon our external environment for supplying us with the necessary stimuli, but we have in varying degrees the power of occasionally providing the stimuli for ourselves. In those patients whose prefrontal lobes have been disconnected or removed it is this ability which seems to be lost while they remain as capable as ever of responding to stimulation from without.

We are unable to agree with Hutton as regards the motor component. We (11) have been impressed with the continuation of the motor component in the psychotic behavior long after it has ceased to have much meaning for the patient. Some patients even continue to recite their previous complaints, but as in a litany, without the surging emotion that previously accompanied the complaints. We have compared the emotion to the fixing agent that prevents a photographic image from fading back into obscurity. Remove the emotion and the image gradually fades. Prefrontal lobotomy bleaches the affect attached to the ego.

Cobb (11a) has theorized constructively about frontal lobe functions, his theories being based more upon studies of frontal lobectomy rather than upon prefrontal lobotomy. He points out that in Rylander's cases, even though only one frontal lobe was sacrificed, there was damage to the other frontal lobe in half of the thirty-two cases, and in fourteen of these personality changes were pronounced, whereas only six of the other sixteen cases where no evidence of damage was shown to the opposite frontal lobe manifested personality change.

Cobb does not believe that foresight is an essential function of the frontal lobes, since conditioned reflexes are a manifestation of a primitive sort of this phenomenon, and they can be found in animals deprived of their frontal lobes, or even in animals with no cerebral cortex. He concludes, however, that the frontal lobes are important in "long-circuiting" actions:

It is this mechanism that allows for an enormous increase in association; it gives higher integration and leads to delayed action. This process of spread is essential for coordination. Its acme is found in the cerebral cortex where stimuli arriving at one receiving station (e.g., the visual "center") spread in innumerable directions to many other cortical areas, awakening associations, habitual responses, memories. . . . This allows the past experience of the individual to affect his behavior, and if there is any distinction between man and "lower" mammals, it would seem to be this: adult man usually looks ahead and acts in the light of past experience; it is typical of his behavior that he "puts two and two together"; even in the highest apes this process is rudimentary. . . . To my mind it suggests that the operation [of prefrontal lobotomy] makes its effect by greatly reducing the number of possible circuits for association. The more destroyed the less "long circuiting" remains. No specific trait or character of man is taken away. The essential point is that the extraordinarily extensive mechanism for association has been reduced.

The other observation of Freeman and Watts that "the symptoms of frontal lobe deficit undergo gradual regression" is also in favor of my theory that the important thing for intellectual function is an immense number of paths for association, unspecialized, but joining specialized areas. Thus a patient who becomes regardless of the opinions of others and hypomanic after lobotomy may later reorganize his personality on the basis of what he has left in the way of association paths. This would explain improved behavior several months after operation. If the frontal lobes were the "centers" for "foresight" or "imagination," such improvement could never occur. The fact that it usually occurs after "prefrontal lobotomy" indicates that other cortical areas with unoccupied association paths can form the sort of reflex pathways that give the person "foresight."

Cobb's views have much to recommend them, but two facts should be kept in mind. In the first place, lobotomy does not interrupt all the pathways, and secondly it does not remove the cortical tissues. Cases of bifrontal lobectomy have shown much more disabling lack of personality organization, based on foresight, than have the cases of frontal lobotomy. The emotional component implementing the ideational processes developed in the frontal lobes concerning the ego and the future is reduced to a point where the ideas no longer harass the patient and he can react in a more flexible fashion to external events. Introspection and foresight are still possible for these patients, but they are difficult, time-consuming, and "not worth the trouble."

A recent British symposium (11b) on frontal lobotomy has also given opportunity for the expression of ideas concerning the functions of the frontal lobes. Rees, for instance, suggests that "functional mental disorder in the terms of Freudian psychology is due to a conflict between the super-ego and the libido, or, to put it in anatomical terms, between the frontal lobes and the thala-

mus . . . Without the frontal lobes there can be no super-ego, without the super-ego no conflict, and without conflict no functional mental disorder." He leaves us with the comforting thought that: "The great majority of mental conflicts are resolved by means of a little alcohol, a night's sleep, bromides, or a change of environment."

Golla (11b) was impressed with the ability of patients to function with progressive improvement after operation. He recalled Horsley's experiments upon apes in which the animals were first trained in bimanual skilled acts and then subjected to successive extirpations of both hand areas with subsequent return of the ability to perform the same acts:

It seems as though the central nervous system can re-orient itself. If it cannot work in one way it will do so in another. We have not done irreparable damage by cutting the "phone system" . . . After a destructive lesion, the central nervous system is not, of course, exactly the same as before, but it is going too far to say *a priori* that any particular lesion will make it impossible for the central nervous system to perform any particular act; it may do it more circuitously, probably not so skilfully, but I think one can say this, that it is up to the opponent of Moniz's operation to show that one has inflicted a lesion of such a nature that the nervous system is unable by any other mechanism to perform the majority or possibly all of the mental operations which it executed before. I do not say they are performed so well, but they may be performed, sometimes a good deal better. If one alters the particular form of imagery used by certain people, their mental operations may be very much improved. I do not think that anyone with a knowledge of G.P.I. (paresis) would believe that there was [following fever therapy] a gradual resolution of the inflammatory process. The patient was exploring fresh, if more roundabout, neural mechanisms and he was adopting more circuitous but sometimes equally efficient ways of conducting his mental processes.

SHOCK THERAPY

The literature on shock therapy has grown to considerable proportions, and more papers are on the way. Early enthusiasm is being tempered by long-term follow-up studies, by studies on unshocked, control patients, and by recognition of harmful effects. The expensive and rather dangerous insulin treatment is being restricted to fewer hospitals and selected patients. Convulsant drugs have been practically abandoned for the simpler and safer electrical method. Kolb & Vogel (12) in a survey of 305 mental institutions reported upon results in upwards of 67,000 patients treated in this country during the years 1935 to 1941. Penrose (13) in a more detailed statistical survey showed the general in-

effectiveness of shock treatment in schizophrenics when they were followed over a sufficiently long period. According to Ebaugh & Johnson (14), insulin does not have a specific curative effect, but may bring about changes that accelerate or facilitate improvement in those who have the constitutional capacity for such improvement or recovery. They go on to mention a number of theories concerning the *modus operandi*:

(1) Insulin induces the oxybiotic processes necessary for detoxication and also an irritation of the cell membranes (Freudenberg).

(2) Metabolism of brain is diminished (Himwich).

(3) Increased permeability of cellular films, exchange of ions, removal of products of metabolism (Spiegel).

(4) Threat to existence, punishment, death and rebirth (Various).

(5) Patient becomes able to turn his affection and his interest to persons and objects of the outside world and so give up his narcissistic isolation. Whether permanent or not depends upon his capacity to endure reality with its alluring and threatening qualities (Jessner and Ryan).

(6) Neither the endocrine phase of the treatment nor brain pathology, nor the question of convulsions nor the soothing, quieting effect, nor failing consciousness, nor the potent psychic shock . . . is alone sufficient to solve our problem (Müller).

We should also quote Abse (15): "By strengthening the resources at the disposal of the ego we can sometimes relegate the conflict to a less dominating position, even submerge it in the deepest strata of the mind." So much for current psychiatric idiom.

Evidence of disturbance of cerebral function consequent upon shock therapy is to be considered in several different categories: anatomical, electrophysiological, chemical, physiological, and psychological.

Anatomical changes.—Most of these are reversible (16 to 20). Petechial bleedings are probably due to head-banging during the convulsions or to severe asphyxia. Ganglion cell changes are chiefly of the chromatolytic variety, sometimes progressing to necrosis with very little reaction on the part of either glial or connective tissue elements. The changes following prolonged hypoglycemia are most notable. The areas of cellular disappearance are usually small and scattered, although sometimes they occur in certain cell layers, particularly the small pyramidal layer. Similar lesions are also found in the basal ganglia, brain stem, and cerebellum. The more recently developed association areas of the frontal, parietal, and temporal regions are most apt to be affected, but

changes in the hippocampus resembling those found in epilepsy are reported. The finer details of the central nervous system, neurofibrils, boutons terminaux, and dendritic expansions have not yet been adequately investigated.

Following convulsive shock therapy, vasodilatation is a striking feature, although limited to an hour or less. In experimental electroshock the congestion is maximal between the electrodes (21).

Electroencephalographic findings.—Disturbances in cortical potentials in the period immediately following shock therapy are often striking. Electroencephalograms reveal disturbed patterns, with delta waves, and obliteration of the alpha pattern. Such waves may persist for weeks and even months after the series of treatments is completed, but according to Wortis (22) clinical improvement is often associated with the appearance of "pathologic" brain waves. Levy, Grinker & Serota (23) found: "In most instances the e.e.g. abnormality and the changes in the sensorium were mutually confirmatory of impaired cerebral function." The occurrence of spontaneous convulsions long after the termination of shock therapy has been reported by Liebert (24).

Biochemical findings.—Chemical studies of importance have been carried out by Himwich (25) and others (25a). "All shock therapies of schizophrenia subject the brain to a period of metabolic depression." As a background it may be recalled that the brain utilizes glucose alone in its metabolism, the respiratory quotient of brain tissue in the Warburg chamber being almost exactly 1.0. Insulin removes glucose from the circulating blood and thereby deprives the nervous tissue of its essential fuel while not causing anoxia of the connective tissues or glandular elements. Thus there is a selective effect upon the neural tissues, and the blood returning from the brain reveals a high remnant of oxygen. Furthermore, there is upon recovery no surge of active metabolism as tested by blood flow or excessive uptake of oxygen.

Convulsant drugs and electroshock also cause diminution of oxidation in the brain tissue probably through generalized anoxia and asphyxia (26). Again there is no compensatory increase of note in the cerebral uptake of oxygen, although recovery of normal metabolic processes is rapid. Simple deprivation of oxygen as carried out by Himwich through nitrogen inhalation would seem to be theoretically the most pleasing and harmless way of effecting the same result, but in his experience is the least successful in

producing any prolonged clinical alterations in his patients. Fever therapy and prolonged narcosis are more or less on a par chemically and clinically.

In order to get better results from shock therapy, Wortis, Terris & Korr (27) have devised means of safely prolonging the insulin coma to as long as twenty hours. This is done by administering 5 per cent glucose in saline solution at a rate of from 3 to 10 cc. per minute, allowing the patient to revive every two hours, and then injecting more insulin. When fever or continued coma in spite of elevated blood sugar shows that the body is unable to burn glucose, large amounts of saline and whole blood are given. Blood transfusion acts in almost specific fashion to interrupt prolonged hyperglycemic coma, but the mechanism is not fully understood.

The prolongation and intensification of insulin shock stem from observations by Wortis & Lambert (28) that a much higher percentage of clinical recoveries is obtained in patients who survive protracted hyperglycemic shock than those in whom this accident does not occur. The conclusion seems obvious that with greater damage to the cortical neurones as indicated by pathological studies of fatal cases, and greater improvement as shown by clinical studies of recovered cases, there must be some relationship between brain damage and mental improvement. Freeman (29) has written of "brain-damaging therapeutics."

Physiological studies.—Gellhorn (30) in a scholarly monograph deals extensively with the physiological alterations in the autonomic system that take place in response to hypoglycemia, as well as in response to anoxia, asphyxia, hypercapnia, and hemorrhage. All of these call into action the sympathetic system. He writes:

During the course of hypoglycemia, the cortical functions suffer first. Associations are performed with considerable delay and simple mental operations such as addition of two digits require longer periods of time. Disturbances of sensation and perception are found. Paresthesias in almost all sense areas are seen and optical perceptions of space (micropsy) are altered. The patient becomes somnolent and disturbances of speech appear. Perspiration and salivation occur as early symptoms and continue during the various phases of hypoglycemia. They indicate a release of autonomic functions from cortical inhibition.

This period of cortical depression passes gradually into a state of primitive motor activity and increased sympathetic discharge. . . In addition to sweating, other signs of central sympathetic excitation such as increased pulse rate, exophthalmus, and pupillary dilatation appear.

Gellhorn shows that the cortex is more susceptible to hypoglycemia by the fact that electrical activity as shown by electroencephalograms may be completely arrested in deep insulin shock. In this state convulsions often occur, a fact indicating their subcortical origin. Furthermore, the injection of glucose stops the convulsions immediately, whereas the cortical action potentials do not reappear for several minutes. Gellhorn emphasizes the importance of the maintenance of a constant internal environment for the preservation of normal brain excitability. "Since convulsions, whether induced electrically or chemically, cause a profound excitation of the sympathetico-adrenal system and a rise in blood sugar, their occurrence in insulin hypoglycemia may be looked upon as a final attempt of the organism to restore homeostasis."

Metrazol has a mild stimulating effect upon the respiration of brain tissue *in vitro* (26), in contrast to insulin which lowers it toward zero. The depression of brain metabolism in metrazol shock is due to the asphyxia and anoxia associated with the convulsion. In both instances, however, there is pronounced stimulation of the autonomic system, particularly its sympathetico-adrenal division, and this, according to Gellhorn, is the only common factor in the two therapeutic methods.

As far as schizophrenic patients are concerned, Gellhorn states:

These observations demonstrate in schizophrenic patients not only a decreased reactivity of the sympathetico-adrenal system, but also a relative preponderance of the vago-insulin system. . . .

If it is correct that the major action of the therapeutic procedures used in schizophrenia involves the stimulation of the autonomic centers and predominantly the sympathetico-adrenal system, and if, in agreement with this idea the psychotic person is characterized by a lack of reactivity of the sympathetico-adrenal system, it seems probable that an improvement or cure of the disease would be associated with an improvement in the reactivity of the sympathetico-adrenal system and with a restoration of the balance between the two branches of the autonomic system.

Gellhorn excludes the hypothalamus from the emotion-producing sphere, showing that it is only the effector portion of the apparatus. Direct stimulation of the hypothalamus, while it gives rise to manifestations of "sham-rage" does not bring on any of the after effects of violent emotional explosions, the repercussions of which are slow to die out in the really frightened or angry animal. Fur-

thermore he might have called attention to the acute panic states that occur in schizophrenia with the spontaneous reverberations in the sympathetico-adrenal system. Such activities are by no means as effective in bringing a patient out of his psychosis as are the induced alterations following insulin shock or electroshock. This author furthermore does not appear to take very seriously the actual damage to the brain produced by the various procedures applied. In shock of any kind, be it traumatic, postoperative, from hemorrhage, or even from emotion, the most delicately balanced intellectual processes are the first to be disturbed. May it not be that the activation of the sympathetico-adrenal system of itself will give rise to certain changes in the central nervous system, at first reversible, and then permanent?

Excitation of the sympathetico-adrenal system is by no means an unmixed blessing if carried to extremes as Freeman (31) has shown. No matter in what way this excitation takes place, there is a consequent drop in blood volume, which, if not corrected, leads to a vicious circle of pathological sympathetic hyperactivity in which the drop in blood volume itself becomes a stimulant to sympathetico-adrenal overactivity. When blood volume gets below the critical stage from any cause the patient is facing death. According to Freeman (32) one of the most reliable signs that this is occurring, and equally important with the presence of thirst and dry tongue, is the subject's lack of mental acuteness and interest in what is going on around him. War is replete with causes of sympathetico-adrenal overstimulation. Heat, cold, pain, loss of blood, thirst, anoxia, and finally rage and fear—all these may be operative.

Who dies through fear first trembles and perspires,
His hairs erect, eyes wide; his inner fires
Then blaze afresh though hands and feet are cold,
And blood turns thick and black as he expires. (Anon.)

Hofmann (33) believes that in shock therapy a higher apparatus is activated which is antagonistic to the vegetative system, but his blood sugar curves do not demonstrate this mechanism. Other authors (34, 35, 36) approach the transcendental.

Psychological changes.—Evidence of damage to the brain in shock therapy is perhaps most striking in clinical reports and psychological studies. Authorities disagree, however, as to the extent and permanence of such damage. Most of them believe it

is evanescent. Levy, Serota & Grinker (23), for instance, call attention to the euphoria and elation and the "organic" type of sensorial defect, and state that the "degree of cerebral dysfunction varies directly with the number of convulsive treatments" and that certain defects may last for weeks or months. Furthermore: "some damage to the cortical neurons was produced so that the convulsive threshold was lowered." Zubin & Barrera (37) testing their shock patients for relearning, recall, and recognition, found all three defective. Under shock conditions the differential between recent and remote learning disappeared. Löwenbach & Stainbrook (37a) emphasized the intellectual disintegration consequent upon electroshock.

The reappearance under shock treatment of certain artificially induced reactions established at an earlier period of existence has been noted both in patients and in animals. Kessler & Gellhorn (38), for instance, produced in rats a conditioned response to a bell and then allowed it to die out through lack of reinforcement. Such responses never recovered spontaneously, but the application of one or more convulsions restored temporarily the inhibited conditioned response. Similarly, Rodnick (39) studied a series of twenty-one schizophrenics with adequate controls. He set up a simple motor habit in each patient and then trained him in another habit which was similar to the first but incompatible with it, thus necessitating the suppression of the first habit. The experimental group was then subjected to metrazol shock and both groups tested for the retention of the habits. There was a higher number of reversals to the older habit in those subjects treated by metrazol. Wittman & Russell (40) did not find memory defects in their treated patients, but these authors stand almost alone. They do say, however, that "if such memory defect occurs (as suggested by Platner as well as by Tooth and Blackburn), it is more than compensated for by the pronounced improvement in interest, attention and social responsiveness on the part of the patient." Which is quite beside the point.

In our experience, one of the essential effects of shock treatment is to make the patient forget. We therefore give shocks daily or even oftener until the patient remains in a somewhat confused condition for several days, unable to remember the names of the physicians or nurses, the day of the week, or the number of treatments. Such forgetfulness, confusion, and inability to pursue

a consecutive trend of thought are temporary. They are to be compared to the splinting effects of a plaster cast applied to a fractured limb which prevents normal mobility as well as abnormal hypermobility of the affected parts. "Splinting of the mind" by shock therapy permits the pathological mental activity manifested by preoccupations, depressive ideas, delusions, and so on, to die out. In cases in which these activities are not too deeply ingrained, the cessation of the repeated insults to the cortex by therapeutic shocks permits normal mental activity to return while the abnormal "hyperactivity" remains suppressed.

Various authors have attempted to determine whether the beneficial effects of shock therapy can be foretold in the individual case. Kisker (41), for instance, concludes that patients will improve if, under conditions of the Rorschach inkblot test, they show lack of concentration, numerous side remarks, good perception accompanied by uncontrolled extensive associations, and an unevenness of performance. Patients who did not improve under insulin shock therapy showed poor perceptions in spite of controlled elaboration and an even performance level. He queried whether pharmacological shock therapy might have brought about any deep restructuralization of the personality pattern or of its underlying dynamisms. Katz (42), furthermore, in similar studies, found that after clinical remission from schizophrenia under insulin shock there were still many indications in the Rorschach interpretations of schizophrenic elaboration. He concluded that there was no complete *restitutio ad integrum* by virtue of shock therapy.

The evidence assembled from the various fields of investigation in regard to shock therapy points definitely to damage to the brain. Perhaps the majority of authors tend to minimize the significance of this and attempt to find some explanation more satisfying to their consciences. There is still a tendency to consider the brain as the "temple of the mind," the "seat of the soul," and the "greatest gift of God," and to decry any suggestion that such a holy structure is being tampered with. The shackles of medieval thought are difficult to strike off. Materialistic philosophy may have gone to other extremes. Erickson (43) quoted one writer who spoke of the frontal lobes as biological luxuries, and an eminent evolutionist who termed them parasitic growths. According to Fleming (9): "The removal of these neoplastic redundancies would

appear to be a therapeutic procedure of value if these statements were true." However, he specifically states further: "We did not 'dash in with careless rapture to mutilate the frontal lobe'." And McGregor & Crumbie (44) hedge with the thought: "We cannot believe that Nature has endowed us with too much brain and left it to the surgeon to correct the error."

It will be granted, we believe, that both psychosurgery and shock therapy have proven themselves of value in the restoration of certain sick individuals to productive existence. It may be emphasized that the brains of these patients have been anatomically indistinguishable from normal previous to the procedure and demonstrably altered after treatment. Various explanations have been advanced in many quarters as to how a person can function more effectively with less brain tissue at his disposal. Hutton (4) has studied some patients before and after prefrontal lobotomy with the Kohs blocks and concludes that the operation simplifies mental procedures:

In order to succeed, the subject must attend to two objects in the external world of reality—namely, the design and the arbitrarily chosen parts from which the design is to be constructed. But suppose the subject's attention is already absorbed by some unrelated personal idea, it would be necessary for him to solve the problem to attend to three things at once—the design, the arbitrarily chosen parts, and his own absorbing preoccupation. In truth the subject will fail not because his abstract attitude is impaired but because he is too abstract.

Lidz, Gay & Tietze (45) contrast schizophrenic and organic deficit states with regard to the Kohs blocks and vocabulary tests.

Damage to the brain, whether by shock therapy or by surgery, reduces the mechanisms available for abstractions. In the case of surgery we believe it is by virtue of the removal of the emotional component supplied by the thalamic connection with the prefrontal cortex. In the case of shock therapy we believe it is due to the damaging effect upon the cortical neurons, thereby breaking the vicious circle of preoccupation-emotion in its intellectual sector. Presumably the damage to the brain in shock therapy is reversible, or at least can be compensated for quite readily. This may explain the fact that remissions after shock therapy are often temporary.

An interesting feature in connection with this discussion of brain-damaging therapeutics is the occurrence of spontaneous recovery in patients who have been treated conservatively. It is

generally admitted that shock therapy is useful more as an agent for hastening the process of recovery in recoverable disorders than for acting as a true curative agent. Such being the case, we might ask how, from the physiological standpoint, the pathological activity of the brain returns spontaneously toward the normal. This is a question, however, that should be asked merely as a check on the enthusiasm of the experimenter and therapist, and not for the purpose of arresting him in the search for new and better methods of therapy.

In closing this section we would call attention to Goldstein's recently published monograph on *The Aftereffects of Brain Injuries in War*. A review of this work (46) is outside of the province chosen for this summary but we desire to stress its significance for physiological psychology.

EXPERIMENTAL NEUROSIS

The subject of neurotic behavior induced in animals deserves fuller discussion than can be given in this review. We propose to submit merely an outline and to refer the student to two monographs and a number of papers published during the past two years. The subject is admittedly controversial, but the lessons to be learned are becoming clearer every day.

Substantially, experimental neurosis was observed by Pavlov in the course of reflex conditioning experiments a quarter of a century ago, when differentiation between positive and negative stimuli was pushed beyond the limit of a particular animal's capacity. Gantt (47, 47a) has pursued and extended this line of work on dogs; Liddell and his co-workers (48a), especially Anderson & Parmenter (48), on dogs, sheep, and pigs; and Masserman (49) on cats. The recent tendency is to get away from the rigid experimental conditions imposed by Pavlov with the light-proof, sound-proof room, the harness and so on, and to study the social as well as the organic behavior of the distressed animal.

Experimental neurosis is a by-product of work on conditioned reflexes. Until it became a study by itself it was an interfering influence, disturbing to the experiment and exasperating to the experimenter, since it necessitated the discarding of laboriously trained animals and at times damaged the experimental apparatus. Only a few animals broke down in this way, seven out of twenty-eight sheep, and three of twenty-six dogs (Anderson & Parmenter).

These animals seemed to be of the "nervous" excitable type even before the conditioning was commenced. When they did develop manifestations of experimental neurosis, however, they retained that tendency for years, even though the experiments were interrupted completely and the animals given long periods in a "normal" environment in which to recover. Attempts at therapy in experimental neurosis had not advanced to any considerable degree until Masserman, applying well-known principles developed in the clinic, showed how these sick animals might be brought to a solution of the conflict and a consequent disappearance of the somatic and social perturbations.

Gantt has advanced the study by the early detection of the breakdown by measurements of autonomic functions (secretory, cardiac, respiratory, and sexual) with the animal under artificial strain, revealing the disturbance long before the appearance of abnormal overt behavior.

The disturbances in the neurotic animal have been summarized by Lubin (50) as follows: (a) hyperirritability: overactivity to stimulation and restlessness during the experiment; (b) inhibitory type of reaction: catatonia, with extension instead of flexion of the stimulated extremity; (c) transfer of motor reaction pattern from one part to another resembling the transfer of neurotic pains in humans; (d) disturbance of diurnal neuromuscular activity, with insomnia; (e) disturbances of respiratory rhythm; (f) disturbances of cardiac rate and rhythm; (g) retention of urine and feces for the duration of the experiment, with frequent, precipitate, uneven evacuation later; and (h) erratic social and emotional behavior: shyness, solitary behavior, varied by states of aggressiveness, biting, kicking, struggling, and resistiveness, some animals losing their sex interest.

The "causes" of neurotic behavior in animals are probably various and incompletely understood. Anderson & Parmenter theorize upon chemical alterations: "Such a long-enduring disturbance of the chemical equilibrium of the nerve cells may involve, among other substances, the ions of sodium, potassium, calcium, and magnesium. Thus for example, a prolonged, even slight, excess or diminution in the concentration of the ions of sodium in the environmental medium of these cells, and brought to bear upon their life processes, may produce prolonged changes in their fundamental functional activity, an increase or decrease

of their irritable properties, so that a general state of hyper-irritability or hypoirritability of the nervous system may result." It is hard to follow this reasoning, since the same experimental procedures may produce opposite reactions not only in similar animals, but in the same animal at different times.

Wolf (51) sealed the eyes or plugged the ears of rats during the nursing period and then noted their behavior later on when, with eyes and ears available for use, they were placed in competition with their control litter mates. He found that the integrated capacity to cope with reality is maintained until a rat reaches a competitive impasse. At this point mature responses disintegrate. The animal retreats to an immature previously conditioned response which formerly secured mastery over the environment. In the process of withdrawal it loses adult functions which were undeveloped during the nursing period. Wolf draws the analogy between this state and human neurotic behavior in which the adult loses highly developed skills in retreating to outmoded but previously serviceable forms of adaptation.

Masserman has advanced our conception of the experimental neurosis in a number of respects. He has repeated the experiments of Ranson on direct electrical stimulation of the hypothalamus and observed the diffuse sympathetic discharge with manifestations of "sham-rage," but has shown that such a reaction cannot be brought about by the conditioning technic, that the response dies instantly when the current is cut off, and that it is possible to handle an animal that is showing all the outward signs of rage without risk of injury. The hypothalamus, Masserman concludes, is only the effector organ for emotional display.

Later, by means of a complicated but superbly conceived series of experiments, he produced experimental neuroses in cats, and studied the behavioral responses to a variety of procedures. Substantially, he produced frustration by motivational conflict, administering a blast of air or an electric shock after conditioning the animal to react positively to a feeding signal. In control experiments he found that mechanical interference with goal-directed behavior produced adaptive extinction of the conditional response, whereas irregular rewards, if anything, tended to crystallize and intensify behavior patterns. Neither procedure produced marked neurotic aberrations such as appeared when the goal-directed behavior was made conflictful by the elicitation of opposing moti-

vations in the animal itself. When the experiments were carried out with adequate motivational conflicts, animals responded by showing a variety of patterns of neurotic behavior. There were phobic responses and counterphobic reaction patterns, regressive behavior, excessive preening, aggressiveness, playfulness, timidity, refusal of food, hiding, attempts at escape, and immobility.

Masserman was particularly interested in therapy, and therefore "treated" his animals in various ways by rest periods, reduction in one of the conflictful drives, "reassurance and persuasion through transference relationships," forced solution, example through the normal behavior of a cage-mate, partial control of the experimental situation by the animal subject, and the opportunity to "work through" the neurosis. Of all the procedures he found that the manipulative "working through" of the conflict by the animal itself was the most productive of permanent alleviation of the disturbed behavior.

The implications of these researches are of greatest importance. While some writers may object to the transfer of conclusions gained from such animal experiments to the problem of neurotic behavior in the human, it will readily be admitted that in the experimental animals under conditions of waiting or frustration there develop: (a) severe and lasting disturbances in activities of the autonomic system; (b) aberrations in the relationships between the affected animal and his mates; (c) difficulties in adaptation with reappearance of more primitive or regressive behavior poorly adapted to the solution of the problem of the moment. Furthermore, the same principles of treatment that have been found useful in cases of human neurotic behavior, have also been applied with almost exactly comparable success in the cases of these animals. The implications are that by further study of the experimental animals, which is already continuing, our therapeutic armamentarium will be correspondingly increased. The subject of shock therapy in animals made experimentally neurotic is already under examination (48), and one may refer to the elimination of neurotic behavior in the chimpanzee by the operation of bifrontal lobectomy as carried out by Jacobsen (52).

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INDUSTRIAL PHYSIOLOGY

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War has greatly increased our appreciation of the importance of the health of the worker as evidenced by the numerous publications on various aspects of industrial physiology from 1940 to 1943. Because of restricted space this review will consider only those containing new experimental or statistical material or new viewpoints. Industrial toxicology, occupational diseases, and fatigue of pilots are not included.

Physical fitness for industrial work.—A certain standard of physical fitness is essential for industrial jobs involving muscular strength and endurance. A widely used classification has been recommended (1): I, physically fit for any work; II, minor defects; III, fit only for certain employments under medical supervision; IV, unfit for any employment. Since 1924 there has been a decline in the rejections of applicants for industrial jobs due to physical shortcomings; the average rate was as low as 4.4 per cent in 1941 (2). Some system of rating in respect to the physical demands of the job has been introduced in 80 per cent of 1,388 plants; these companies had a lower average rejection rate than those without job classification (2). These methods permit conclusions of general statistical nature, for instance, that the percentage of class I workers diminishes, because they are inducted into the army (3, 4). Clinical methods are useful for screening the physically unfit (negative selection). The importance of regular clinical check-ups has been repeatedly emphasized, but clinical methods are not adequate to differentiate between those who are fit (positive selection). To a certain degree this seems to be true also for functional tests. Several investigations were performed to determine the significance of physiological functions for physical fitness. In thirty-three recruits from seventeen to twenty-one years there was a complete dissociation between the improvement of performance (three mile run) and improvement of vital capacity (absolute and postexercise drop), breath holding time, and resting and postexercise pulse rate during six months of military training (5). Observations (6) that repetition of exercise in weekly inter-

vals may accelerate recovery of pulse rate without change of performance might be interpreted as corroborating these findings. Training improved the performance (measured in terms of maximum rate) of fourteen subjects by 47 per cent, associated with too slight an increase (5 to 10 per cent) of efficiency, oxygen intake during work, blood lactic acid, and oxygen debt to account fully for the improvement of performance during training (7). The increase of performance by training is much greater when measured in terms of endurance at constant rate; under these conditions an improvement up to 2,500 per cent was reported (8). No changes were found (9) in forty-three out of forty-eight athletes after an entire season of training, when they were in peak condition. Wachholder (10) found in running at a speed between one hundred and three hundred steps per minute after an initial increase of pulse rate, a considerable retardation (explained by excessive vagus impulses) which was less pronounced in the physically less fit. However, in some highly efficient athletes there was no initial increase. Taylor (11) investigated whether there is any critical change of the trend of physiological functions, when the work load (bicycle ergometer) was continuously increased until the subject was forced to quit from exhaustion. The exhaustion trends of metabolic and circulatory functions were not uniform. Total ventilation most often became markedly excessive, so that the concentration of carbon dioxide in alveolar and in expired air decreased. It is concluded that the increase of pulmonary ventilation and related functions is the most reliable objective index of approaching exhaustion. If the eleven subjects were grouped according to increasing crest loads, at which exhaustion occurred, there was some parallelism to the increase of the oxygen intake per kilogram body weight and a less pronounced parallelism to the individual efficiency. It is clear that the capacity for physical work will be highest in those who have a high level of maximum oxygen intake associated with a high efficiency. In fact, consideration of both efficiency and maximum oxygen intake results in a better correlation with the crest load than do any of these functions alone. Dill (12) believes that simple functional tests, such as the Schneider test, are not adequate to determine physical fitness. Henry (13) discusses several possible explanations for the lack of agreement in the literature as to the relative validity of the various functional tests. It is claimed that a higher score of a "work

index," the essential variable of which is the sum of maximum pulse rate and blood lactate, would represent greater fitness (14). However, there is no consistent relationship between accumulation of lactic acid and fatigue (15, 16, 17). The "work index" is not proposed as a practical routine test of physical fitness (14). Until better correlations have been established, caution in the interpretation of physical fitness tests is advisable. Due to the lack of consistent relationship between physical capacity for work and functional tests, the measurement of performance in terms of maximum speed, load, or endurance might be superior (18). The percentage of recovery, calculated as difference of performance between a first and a second work period, separated by a given interval, shows less variability than either the first or second work period (19, 130). Since the recovery is less complete when the first work period is higher at the same interval, this recovery index diminishes in training. When comparing different individuals, it can only be used as fitness index when the first work period is about the same. If the interval between two work periods is too long (ten to seventeen minutes), the second performance might be higher than the first one (20). This phenomenon is associated with an increase of muscle action currents. The action currents reach the resting value only after thirty minutes; at this time a second work period shows no significant increase. The higher performance after ten to fifteen minutes recovery is explained by facilitation processes. Training levelled the individual differences in running performance (5). In industrial work training has usually the same effect in rather simple tasks, while it tends to increase the individual differences in more complicated operations (21).

Although in laboratory experiments the work performance in itself appears to be at least as significant for the study of fatigue as the concomitant physiological functions, it is doubtful whether this can be generalized on industrial performance (output). Industrial output depends very much on what is expected from the worker, so that output may increase at the end of the day in spite of fatigue (22). Output in industry is influenced and interfered with by psychological, social, and socioeconomic factors (23), which laboratory experiments tend to eliminate. In conveyor belt work with fixed rate fatigue might manifest itself rather in an increased percentage of spoiled work than in diminished output.

Decrease of output might indicate accumulated excessive fatigue, as shown by the experience in England after the fall of France (24) or during the First World War (25). This does not mean that industrial output is an adequate method for the study of fatigue in more normal conditions.

Alternating short rest pauses may increase endurance enormously (26). The oxygen consumption does not fall during the short rest pauses, but remains at a steady state, which is, however, much lower than in uninterrupted work. This means that formerly "heavy" work can be changed to "moderate" work by introduction of frequent short rest pauses. The favorable effect on endurance is associated with improvement of the efficiency, which is still more pronounced when the short rest pauses are spent in sitting position. Standing not only increases fatigue by cerebral anemia and drop of cardiac minute volume, but also produces local fatigue of the feet, which frequently interferes with production in jobs which require prolonged standing (27, 28, 29). The endurance in hard exercise (bicycle ergometer) was decreased after donation of 500 cc. blood for ten to twenty days, while types of anaerobic work (duration up to one minute) were not influenced (30).

Although anthropometric measures show definite correlations with athletic performance (4, 17, 31), they have no practical value for selection of industrial workers (21, 32), perhaps, with exception of very few excessively heavy jobs.

Several years ago Donaggio (33) reported a "fatigue" reaction; thionine solution (0.1 per cent) plus 4 per cent ammonium molybdate, added to protein-free urine, produces precipitation, which is less pronounced or missing after exertion. His findings were confirmed by several authors (34 to 37), while others (38) failed to find any consistent relationship between the degree of the Donaggio reaction (although present after exercise) and the degree of effort and fatigue. The Donaggio reaction indicates increase of permeability of kidney capillaries (37, 39). Replacement of the original Donaggio method, which includes many sources of error, by chemical determination of polypeptide nitrogen in urine, gives more consistent results (39, 40). The increase of permeability of capillaries in fatigue would be in good agreement with Eppinger (41) and Kaunitz's work (42).

One of the most urgent questions of industrial physiology is

the increasing occupation of women in industry. In 1942 sixteen million women were working in this country, and the expansion of industry in 1943 can only be accomplished by increasing the number of working women. The only difference between seventeen women and thirty men in the response to moderate exercise (walking) was a more rapid and higher increase of the pulse rate in women (43). The endurance in running of women was only half that of the men. The maximum pulmonary ventilation, oxygen intake, and the respiratory quotient was higher in men, but all variables showed considerable overlapping. When the eight best women were compared with the ten poorest men, no significant differences could be seen. For industrial physiology the insignificant differences between men and women in moderate work have greater importance than the differences in types of hard work far exceeding the average muscular effort in industry. Out of nineteen hundred different operations in twenty-one key defense industries, only 331 were found to be unfit for women (44). A similar proportion is reported by Harvey (45). In hard agricultural work, performed at high environmental temperature, the performance of unskilled Indian and Bantu women laborers is only half that of men (17). There were no investigations on pregnancy and work during the period covered by this review, but recommendations have been made in several editorials (46, 47, 48). All these recommendations are preliminary because of lack of experimental material (49). There was no evidence for racial differences of physical efficiency in a large body of material (17, 31). In the experiments of King *et al.* (50) the performance of a group of negro subjects on the bicycle ergometer was superior to a group of white subjects.

The employment of older people is not only important for the present emergency conditions, but also for the future, due to the continuous age shift in the population. It is estimated that within forty years about 40 per cent of the total population of this country will be over forty-five years old (51). In nine thousand steel workers the average merit rating showed a maximum at thirty-five years and a continuous decline with age (21). The capacity to do anaerobic work (ability to accumulate lactic acid) is diminished with age (52, 53), and the same is true in regard to the maximum intake of oxygen (54). Dill believes that this is due to the inability of older men to increase the pulse rate to the same extent as young-

er men can do. Clinical evidence speaks against this assumption. The rate and distribution frequency of tachycardia, even in pathological conditions is not materially affected by age. Willius (55) recommends relaxation and rest rather than recreational exercise in the advanced years of life. Although the tolerance of the central nervous system against fatigue from muscular work is diminished in older men and women (56), the ability for mental work and for fine muscular coordination (precision work) is not less in women and is obviously not or only slightly influenced by age (51, 57).

Fatigue of the central nervous system.—It is estimated that in about 80 per cent of all jobs in industry muscular effort is slight or moderate, so that general fatigue is due to fatigue of the central nervous system.

It depends very much on the type of work whether fatigue of the sensory or of the motor centers is more significant. Fatigue of the motor centers is more pronounced in types of work with pre-vailing manual components, although even in reading there is a certain degree of muscular activity (58). There is little or no correlation between fatigue of motor centers and fatigue of sensory centers in different types of work (59), in pathological conditions (60, 61), and after administration of drugs to relieve fatigue (59, 62). This agrees with Tiffin's conclusion (21), based on considerable material, that the correlation between muscular skills and mental skills is very close to zero. There is even an independence between different motor functions, so that any theory of general motor ability appears to be ill-founded.

A convenient method to investigate the state of motor centers is the measurement of the maximum number of finger movements by means of a tapping test (63). The performance of this test does not depend on any peripheral function (metabolism, circulation). The drop of the tapping rate in fatigued truck drivers is greater than the change of any other of nine applied psychomotor tests or of the fusion frequency of flicker (64). Indeed, the manual component in driving, i.e., holding the wheel for many hours, is considerable. Also in laundry workers, the decrease of the motor frequency exceeds that of the fusion frequency of flicker (59). Although fatigue of motor centers is important for the actual performance, fatigue of the sensory centers appears to be more important for the general sensation of fatigue. While fatigue of

motor and of sensory centers are not related to one another, there is some spreading of fatigue from one to other sensory centers (65, 66).

The fusion frequency of flicker, which indicates the excitability of the retinocortical system, was used to measure fatigue of the central nervous system. In office, laboratory, and dispensary work the fusion frequency of flicker was lower in the late afternoon than it was in the morning (67), and it decreased in truck drivers parallel to the hours driven (68). A decrease of the fusion frequency in fatigue was also found by Henry (69).

In 90 per cent of forty-five subjects, the fusion frequency was depressed after exhaustive muscular work and increased after light or moderate work (56). This shows that hard muscular work would also produce a certain degree of central nervous system fatigue, while light or moderate exercise, performed during pauses, especially in sedentary occupations, would improve the functional state of the central nervous system. These findings substantiate an editorial comment (70) that physical training of student soldiers ought to be carefully controlled to avoid interference with the educational program. Ward (71) found, as a result of the recent production speedup, an increase of minor symptoms such as loss of weight and appetite, increase of pulse rate and low blood pressure, tremor of outstretched hands, pallor, emotional instability, etc., which disappeared after a period of rest away from work.

Vision and work; visual fatigue.—For industrial work vision is the most important of all sensory functions. There are, however, large differences in regard to visual requirements in different jobs. Much common labor can be performed with a visual acuity of only 20/200 (72). Only corrected vision should be considered for industrial employment (72). It has been estimated (73) that 400,000 industrial workers in this country have visual defects not correctable and that at least one million have moderately reduced visual acuity. In twenty-six out of thirty-four large industrial plants visual examinations were performed and job analysis for visual requirements carried out in only eleven plants. Kuhn (74) found 62.8 per cent with satisfactory vision and 5.4 per cent satisfactorily corrected with glasses in ten thousand steel workers.

In 194 looping hosiery workers (21), an operation requiring continuous critical vision at an average working distance of eight inches from the eyes, there was an inverse relationship between

visual acuity at a distance of twenty feet and performance, i.e., those operators with poorer vision were quite consistently better producers. In other words, a far distance acuity test, such as usually performed in routine examinations, would select poorer operators and reject better ones. Testing of near distance vision (at thirteen inches) was also not satisfactory, because all operators had such keen vision that it was impossible to differentiate among them. The focus posture test, measuring the tendency to focus closer or farther away than a test stimulus at sixteen inches, yielded better results: operators with a tendency to focus closer showed higher average production. There was no correlation between far and near distance vision in 3,512 employees. It is advisable to investigate in addition to distance acuity (*a*) near distance acuity, (*b*) depth perception (stereopsis), (*c*) color discrimination, and (*d*) postural characteristics of the eyes (phorias) at different distances. In workers engaged in assembly of small electrical parts, those who failed in the vision tests (near and far distance acuity, phoria, stereopsis) had higher average output, but those who passed these tests, except far distance acuity, had a higher rating of quality. It is assumed that those workers with better near vision observed and corrected their own mistakes more frequently, i.e., they did better work at the expense of speed.

In one hundred and fifty tin plate inspectors, classified into three groups of visual performance, the accuracy of detecting appearance defects was lowest in the poorest vision group, while the same group showed higher accuracy in detecting weight defects. In twenty-three clerks no relationship was found between hourly production and vision, but those with poorer vision made more errors. A group of six thousand steel workers, unclassified as to the job, were rated as high (2,045 employees), medium, and low (2,096 employees) in regard to job efficiency. However crude this system of classification may be, the difference between the high and the low rated group may be regarded as significant. The far distance acuity was the same in both groups, while near distance acuity, depth perception, and especially color vision were better in the high rated group. It seems that color vision might be more important for job efficiency of steel mill workers than hitherto accepted (75).

Davidson (76) holds that stereopsis is more important for many occupations than visual acuity. Normal depth perception

(twenty seconds of arc) should be demanded for crane operators, carpenters, workers on elevated structures, machinists, filing clerks etc. He found no correlation between visual acuity and depth perception. Culler (77), on the other hand, holds depth and color perception less important for industrial work, but he emphasizes the importance of far and near distance acuity, visual field, and eye muscle coordination. He proposes a coefficient of visual efficiency combining these functions. In this coefficient, near distance vision is evaluated twice as much as far distance vision. He gives a table for suggested requirements of vision for various industrial occupations in terms of this coefficient.

Obviously, the visual requirements for different jobs can only be established by comparison of performance efficiency and visual functions. Tiffin (21) found among seven thousand employees of a steel mill the far distance acuity significantly high in crane-men; near acuity significantly high in foremen, clerks, and machinists and low in laborers. Incidence of normal phorias for near distance was significantly high in clerks and for far distance high in hookers; color vision significantly high in foremen and clerks; depth perception high in foremen, electricians, and machinists and low in laborers. This material shows that significant occupational differences do exist, even after elimination of age trends. This may be due to a natural process of selection and elimination, or to influence of the work on the vision. Tiffin presents interesting evidence for the latter possibility (21). The far distance acuity of looping hosiery workers was consistently diminished during fifty months of experience, associated with an increasing tendency to focus closer, as shown by the focus posture test. Kuhn (78) tried to replace this influence of occupational training by providing special spectacles, with an optical effect of removing the work farther from the eyes. Loopers who wore these spectacles increased their production by five per cent within eight weeks, compared with a control group without spectacles. The progress of training, measured in terms of production efficiency, was also accelerated.

Most hand movements are performed under visual control, hence eye-hand coordination is an important element of productive efficiency. Tiffin (21) presents an interesting exceptional example of how dissociation of vision and motor coordination may improve performance. In the majority of a group of metal sheet inspectors, studied by means of motion pictures, the eyes tended

to follow the movements of the hands. The accuracy ratings and production records were consistently higher for those inspectors, who were scanning the motionless sheets on the left or right pile, while the sheets were moved from one pile to the other without eye control. In the first (natural) way the accuracy is lower because it is difficult to see details in moving objects, while with the second pattern the scanning periods for detecting details are greatly increased. After this study, the inspectors were trained to work according to the second pattern. This new system reduced very considerably the time to reach peak performance.

Visual work (sorting of rice, reading, sewing) increased the threshold of electrical stimulation of the eye, determined by the appearance of phosphenes (79). After the work, the values slowly returned to normal. The depression of excitability is especially pronounced in types of work involving the motor apparatus (accommodation, eye movements). Also recognition of letters at dim illumination decreases the excitability after a very short time. The time of fading of after-images is markedly increased after types of work involving visual effort (80). The recovery time of visual discrimination, measured after exposure to glare, was prolonged in fatigued truck drivers (81). The fusion frequency of flicker could also be used to measure visual fatigue. The drop of the fusion frequency was much more pronounced in laboratory work including three hours' work with the microscope than in laboratory work without use of the microscope (67).

Precision work, performed for eight hours at artificial illumination with incandescent lamps, produced a delay of dark adaptation, which was not observed or to a lesser degree when a part of the red and blue radiation was eliminated by a new type of bulb (82). Also in welders, occupied in the day shift, there was a tendency of delayed dark adaptation speed at the end of the working day, which was reversed in the night shift workers, probably due to the different brightness of the environment (83). Since eye-strain increases the automatic blinking rate, this simple procedure can be used to measure visual strain or comfort (84).

Auditory fatigue.—Exposure for thirty minutes inside a boiler during repair work or cleaning produces a hearing loss of thirty to forty-five decibels (at a frequency of 4,096 cycles) for several hours (85). The same is true for the noise produced by aviation engines; the hearing loss parallels the duration of exposure (86). The re-

covery of threshold in riveters after a full day's work may take fifteen hours (87). There is agreement in regard to the cumulative effect of noise, finally resulting in permanent hearing loss. Dry cotton plugs or still better cotton plugs saturated with mineral oil, to be introduced into the ear canal, are recommended for protection (88, 89). The recovery of acoustical threshold is considerably accelerated when the lunch pause of one hour duration is spent in noiseless surroundings; also the increase of threshold at the end of the working day is much less under these conditions (90). Auditory fatigue is located in the acoustical centers, above the centers of the tensor reflex (91). During a continuous loud tone there is no rise in threshold of the tensor tympani reflex and no summation effect, in contrast to the acoustical threshold. It is concluded that fatigue of the tensor reflex does not play any important role. Auditory fatigue may be exaggerated in neurasthenics (91). Reduction of the noise level from seventy-five to fifty decibels in a large office increased the output and diminished errors, absenteeism, and employee turnover of typists and machine operators (92).

Heat.—A thorough investigation into the relative importance of the different avenues of heat loss was performed on two unclothed subjects at different working rates (bicycle ergometer) and environmental conditions (93). The heat loss by convection is greatly increased by the process of pedalling up to the rate of thirty revolutions per minute equivalent to the cooling power of air movement of 40 cm. per second velocity on the resting subjects. This might explain the fact that under certain conditions of work at high environmental temperature the subject feels more comfortable at work than at rest (94, 95). The convection loss of even rather high air movements, superimposed on that of body movements, is relatively slight, but it might be more significant for operations with minor manipulations. The radiation loss decreases rapidly when wall temperatures exceed 15°C. However, air temperature is much more important than mean radiant temperature for the sensation of comfort. Increased sweat secretion with consequent heat loss by evaporation is the most effective mechanism for increased heat dissipation. At 21°C. air temperature the thermal reactions of the unclothed subject are in balance with a metabolism of 350 kcal. per hour. At equally high metabolic rate, the radiation loss of the pyknic subject was markedly higher

than that of the leptosome subject who compensated this disadvantage by a higher evaporation rate. Sensation of greatest comfort occurs at 28°C. with the resting subject and at 16° during work (with a metabolism of 350 kcal. per hour), i.e., about 2° below the point where active sweat secretion begins. The advantage of heat dissipation of a large stout man could not be confirmed for grade walking and running on a treadmill (96). In these types of work, involving the movement of the body weight without performance of "external" work, the performance is naturally larger for the heavier individual. The heat production related to body surface was 21 per cent higher in the heavier subject, the efficiency (cal. per mkg.) being the same in both subjects. Therefore, the heavier man has to store heat in conditions where the small man can easily dissipate heat and attain balance. It appears that it depends entirely on conditions of work whether the heavier or the lighter man will be superior. The findings obtained with the bicycle ergometer seem to have greater significance for industrial work, where a certain amount of external work is required rather than locomotion.

Negro sharecroppers were superior to white sharecroppers in a type of work, exceeding seven times the basal metabolic rate, performed for two hours at a temperature of 85° to 90°F. and eighty per cent humidity (97); the rectal temperature and the pulse rate of negroes increased to 101°F. and 150 beats per minute, that of white sharecroppers to 102°F. and 170 beats. There were also differences between a group of northerners, not accustomed to the humid heat of southern Mississippi, and a group of acclimated white sharecroppers. The authors hold that high temperature and humidity may aid rather than hinder performance of anaerobic work (duration of a few minutes). Thorough investigations have been performed (98) to determine the critical points, at which the majority of people would show no deleterious effect at the end of an average working day for varying climatic conditions and intensity of work. Of several physiological functions pulse rate and especially the body temperature were chosen as the most significant and reliable indices. The authors hold that 1½°F. increase of body temperature should be the limit for work in industry. On the basis of their results they present charts and tables which show the expected rise in body temperature related to effective temperature, metabolic rate (intensity of work), length of

exposure, etc. The increase of body temperature and pulse rate with increasing "effective temperature" shows little variation with different relative humidities, in contrast to the relations in the curves plotted against dry temperature (up to 140°F.). This means that wet bulb temperature and especially "effective temperature" are more important for comfort as well as for physiological response than dry bulb temperature. The authors found also a pronounced increase of leucocytes after exposure to heat; they believe that permanent work at high environmental temperature could possibly exhaust this function and lower the resistance power against infections. There is no clinical evidence to support this conclusion. Workers may be kept free from body temperature rise, excessive pulse rate increase, and from perspiration with a blast of cool air or by ventilating their clothing with cool air up to a dry bulb temperature of 112° and an effective temperature of 95.1° (99). For this purpose, a rubber hose was connected to the back of the worker's coverall suit. Although this arrangement requires somewhat lower temperature to attain the same cooling effect as with blast air, the volume of ventilation is eleven times less.

The conclusion that the effect of heat parallels the effective temperature rather than the dry bulb temperature is contested by Australian authors (100). The effect of a hot wet (87.5°F.; 87 per cent humidity) and hot dry (109°F.; 38 per cent humidity) atmosphere at the same effective temperature on the increase of pulse rate during work (marching, weight lifting) is the same only when ample water is given. When only half replacement of water loss is given, the pulse rate is higher in hot dry temperature, and this discrepancy is still more manifest when no water is given. Saline solution improves the cardiovascular reactions only in hot wet not in hot dry temperature (100). Also sweat and chloride loss (101) is greater at hot dry temperature. Substitution of larger amounts of fluid given infrequently, by frequent smaller amounts is of benefit only in hot dry temperature. The same authors found a long term acclimating effect by comparison of Queensland with England's subjects, while during the three weeks of experiments no significant change of response was observed in any given subject.

Nutrition and work.—No investigations on the effect of different standard diets on industrial workers under controlled condi-

tions have been reported. The necessity of such studies has been emphasized (102). Our conclusions, therefore, are largely based on results of laboratory investigations and surveys. There is no question that a considerable recovery from preceding work may occur during the lunch pause. The drop of fusion frequency of flicker during the working day was interrupted or reversed during the lunch pause in 85.6 per cent of sixty-nine experiments in fourteen workers employed in types of light muscular work (103). According to Haggard & Greenberg (104, 105) carbohydrate-rich food intake between meals seems to alleviate tiredness and improves efficiency, parallel to the increase of blood sugar. Welder objects to additional carbohydrate intake, because it might increase the vitamin demand and lead to relative vitamin deficiency, thus increasing fatigue in the long run (106). Hellebrandt & Karpovich (107), reviewing the material up to 1940, conclude that extra carbohydrate is advantageous only in prolonged hard work. Ivy (108), commenting on the improvement of output of workers in a shoe factory by additional intake of cake and milk during forenoon or afternoon, points out that no controls were made with flavored cellulose cookies or flavored water. On the other hand, Jokl *et al.* (109) found three meals a day superior to two meals a day in regard to physical efficiency in twenty-seven well controlled experiments. Also Bristol (110) reports good results on the working capacity by midshift feeding. It has been repeatedly demonstrated that drop of working capacity is an early subclinical symptom of vitamin B and vitamin C deficiency. The effect of vitamin B (notably B₁) deficiency on the working capacity is much more pronounced in men during hard physical work (111) than in sedentary workers (112). Vitamin B deficiency decreases the capacity for repeated and sustained work, associated with an abnormal increase of pulmonary ventilation. A daily intake of 2 mg. thiamine alone will not maintain physical fitness in manual laborers, but brewers' yeast appears to be a complete and adequate supplement for a diet grossly deficient in vitamin B complex. According to experiments on guinea pigs, physical work also increases the vitamin C demand (113). On the other hand, experimental vitamin A deficiency for a period of six months did not decrease capacity for physical work (114).

Most authors agree that the average diet of a very large percentage of industrial workers is unbalanced or insufficient in re-

gard to vitamin B or C content (115, to 120), especially in the low income group (115), oilfield laborers (121), in the southern districts and among negroes (122, 123). The view (116) that sub-clinical vitamin B deficiency could account for breakdown, fatigability, and a certain percentage of absenteeism is supported by experimental evidence that in four trained subjects diets with about one-third of the recommended daily requirement of vitamin B complex produced fatigability and reduced maximal work performance. Such degree of deficiency might be found in about one-third of the United States population (124). Cowgill (125) reports that women made as a rule poorer selection of foods than men, a habit which perhaps might decrease exercise tolerance and resistance. On the other hand, no clinical or subclinical symptoms of vitamin A, B, or C deficiency were found in a group of 1,265 workers (126).

If there is a widespread vitamin B or C deficiency, it should be possible to increase working capacity by surplus of vitamin supply in a large percentage of normal people, given in addition to the average diet. Broese (127) found increase of mechanical efficiency in normal subjects after administration of thiamine and fructose, but not after fructose alone. However, there was no improvement of five different types of muscular performance in twelve normal subjects after prolonged intake of a large surplus of vitamin B complex (6), and these findings are corroborated (128). There was no significance difference in static work between a group with high and another with low vitamin B₁ supply (129). Foltz *et al.* (130) failed to find any immediate effect of intravenously injected vitamin B complex on recovery from fatigue. However, vitamin B complex surplus produced a marked increase of the fusion frequency of flicker in eight of twelve subjects, paralleling a diminution of subjective fatigue (6). This might show that the vitamin B content of the average diet of workers, employed in light manual work, is sufficient to maintain muscular performance, but that the tolerance of the central nervous system might be increased by vitamin B complex surplus. There is agreement that vitamin C surplus does not improve muscular performance (128, 131, 132), although it is claimed that it diminishes muscle pains after hard work (132). The favorable effect of vitamin C surplus on muscular performance of guinea pigs (133) and frogs (134), and of vitamin B complex in rats (135)

cannot be generalized on man. Vitamin A surplus did not improve the speed of dark adaptation in welders (83). Against the claim of beneficial effect of gelatin intake on muscular performance (136, 137), there is agreement that aminoacetic acids or gelatin do not increase the capacity for muscular work (8, 50, 138, 139, 140).

Effect of drugs and hormones on fatigue.—Routine use of drugs to increase performance of industrial workers cannot be recommended; the transitory increase of performance would be followed by an increased need of recuperation. No sustained effect could be expected (141). However, in the present emergency conditions the necessity of finishing a job in a given time or of doing overwork in spite of fatigue is not uncommon. Only under these exceptional conditions should stimulating drugs be given. The work during the last two years concerned especially the effect of amphetamine (benzedrine) and desoxyephedrine (pervitin). The literature up to 1940 has been recently reviewed (141, 142). The effect (relief of fatigue) of both drugs is similar but pervitin appears to have less side effects and requires lesser dosage. It is known that both drugs are widely used in the German army. Staub (143) recommends it for motorized troops of the Swiss army. Fatigue of motorized troops is primarily fatigue of the central nervous system, similar to that in many industrial jobs. Foltz *et al.* (144), using the double work period, found no significant influence of 10 mg. amphetamine or $\frac{1}{2}$ gm. caffeine on performance and recovery of a rapidly exhausting work (stepping up and down a wooden stand carrying a load of one-third of the subjects's body weight) in twenty-three untrained subjects; in trained subjects (bicycle ergometer) caffeine increases performance and accelerates the recovery (19, 145); desoxyephedrine increases the performance of the first working period, but does not improve the recovery, while amphetamine has no effect on performance of the first and the second working period nor on recovery (145). In a prolonged work with a type of Mosso finger ergograph (the single work periods being interrupted by rest pauses of thirty minutes) there was an increase of performance for two to three hours after administration of 10 or 20 mg. amphetamine instead of the normal decrement (146), paralleling an increase of the amplitude of the patellar reflex. The effect of 0.2 gm. caffeine was less pronounced. The discrepancy between both experimental series may be explained with the difference of stand-

ard work used. Fatigue in the hard standard exercise test (144, 145) depends very much on circulatory and respiratory function, while fatigue with the finger ergograph depends primarily on the central nervous system (Mosso). Administration of amphetamine (58) as well as of desoxyephedrine (61) increased the maximum frequency of finger movements. This test is related to the frequency of motor discharges, and there is little interference of peripheral functions. There was also a pronounced increase of the fusion frequency of flicker; the drop during the working day was abolished or even reversed, parallel to the relief of subjective fatigue (61, 147). Kohn-Richards, corroborating these results, found the desoxyephedrine effect more prolonged than the amphetamine effect. Even inhalation of desoxyephedrine is effective (103). It seems that both these drugs are useful for relief of fatigue of the central nervous system, while the effect on muscular fatigue is not as safely established. While methyltestosterone improved muscular performance in castrates and eunuchoids (148), it was ineffective in normal young men (149). Obviously, no influence of additional hormone intake could be expected in subjects with normal sex hormone production. In older men (between fifty and sixty years), in whom a diminution of the sex hormone production may be assumed, intake of methyltestosterone improves muscular performance as well as the fusion frequency of flicker (150).

It is of some practical importance whether the widespread use of sulfa drugs for treatment of chronic infections impairs the working capacity. Sulfanilamide reduces the capacity for mental as well as for hard muscular work, due to interference with the carbon dioxide removal (151). Sulfathiazole and sulfadiazine, which have no effect on carbonic anhydrase *in vitro*, can be safely administered in doses up to 4 gm. per day without impairment of the capacity for mental or muscular work (152), but both drugs, especially sulfadiazine, disturb ocular muscle balance and depth perception (153).

Rehabilitation.—Due to the shortage of man power, employment of physically handicapped people has become an urgent question. Most valuable recommendations for the employment of physically handicapped are presented as disability placement code (45, 154), based on a detailed job analysis and extensive surveys in government plants considering the great variety of factors involved in industrial work. This manual concerns mostly persons

with orthopedic handicaps (estimated to be a total of approximately 2,500,000 in this country), persons with vision defects, and persons with hearing defects (approximately 65,000 totally deaf, 60,000 deaf mutes, and 1,547,000 "hard of hearing"). There are also some data on the employment of persons with tuberculosis (680,000) while very little has been done to effect placement of persons with heart disease or arterial hypertension in governmental industrial plants. From observation of 40,000 workers in one thousand operations in twenty-five Philadelphia industries, it is concluded that about 25 per cent of the jobs could be performed by persons with heart disease without impairment to their health or their jobs (155). Rejection for employment should depend solely on whether the employment would impair the worker or the work (156). About 70 per cent of rejected persons with cardiovascular disorder are probably able to work at something (156). The number of persons with heart disease (estimated 3,700,000) far exceeds the number of persons with orthopedic handicaps. The number of persons with chronic internal disorders is estimated at approximately 11,000,000; this source should be regarded as a great potential reserve. A rather large experimental material on work tolerance of persons with chronic disorders has been recently reviewed (157). Reduction of working capacity is fairly well related to the impairment of definite physiological functions, as revealed by exercise tolerance tests. Such data should be used for rehabilitation purposes, for instance, mechanical efficiency as most significant index for patients with hyperthyroidism, oxygen debt or oxygen utilization of the exhaled air for patients with cardiac or pulmonary disease, respiratory quotient or blood sugar response in patients with diabetes. Patients with hyperthyroidism should avoid speed work. Hitherto, it was assumed that a subject with heart disease would be able to do satisfactory mental work, requiring only a slight increase of oxygen consumption. However, decrease of the fusion frequency and of the tapping rate reveals also a decreased tolerance of the central nervous system to fatigue (60, 62). Therefore, persons with chronic heart disease should be employed in work requiring no overaverage physical or mental effort. The same is true for patients with hypothyroidism (59). The exaggerated fatigue in these patients may be successfully treated with thyroid preparations (158). The statistical material on the rehabilitation of persons with chronic heart disease is scanty. Out of twenty-nine soft coal miners with chronic heart

disease none was seriously incapacitated (159). The work requires no high metabolic rate, but a pronounced static component.

The incidence of arterial hypertension (in 5,433 workers) is so high that it should not be considered as reason for rejection of employees (160). Even after attacks of coronary occlusion about 50 per cent of laborers, 66 per cent of the office workers, and 80 per cent of professional persons resume their work. The percentage decreases with age and repeated attacks according to observations on 1,286 cases (161). The same authors found the return of exercise tolerance to be associated with good clinical recovery (162). Since many patients with cardiac disorder respond to exercise with exaggerated pulse rate, treatment with digitalis, which prevents this response, might increase work tolerance (163). Lake *et al.* (164) studied the incidence of arterial hypertension and varicose veins in 536 persons employed for ten years or more, subdivided according to their work into sitters, standers, walkers, and stair climbers. The incidence of arterial hypertension was highest and that of varicose veins was lowest in the stair climbers (delivery men, etc.); otherwise there were no significant differences. The incidence of varicose veins among sitters was the same in male and female workers but in all other occupations the rate was higher in women.

It is known that moderate work is not injurious to persons with controlled diabetes; on the contrary, it may decrease the insulin demand. There are about 660,000 persons with diabetes in this country. Nevertheless, there is a lack of statistical material (165). The Bell Telephone Company of Pennsylvania employs an unusually large number of diabetics with a rate of absenteeism not exceeding that of other employees (166). The production, lost time, and accident records of employed handicapped workers may be better than those of normal workers (155, 167). Chronic exaggerated fatigue is a very important problem of rehabilitation. It may be the first manifest symptom of various disorders (157). It is observed in ill-nourished youths, who may be markedly improved by military training (5), while Abrahams (168) found the results of physical therapy disappointing. Postinfection neurosis may impair working capacity for a long time, and overwork may prolong the process of recovery (169). All other causes excluded, there remains a group with increased fatigability due to constitutional inadequacy, especially of the nervous system (169). We have several subjects under observation with complaints of excessive

fatigue, associated with subnormal fusion frequency of flicker without any other disorders. Increased fatigability might be due to psychological factors resulting from maladjustment. Psychiatric analysis and treatment of such cases may produce amazing results (23, 170). Treatment of psychosomatic disorders in one hundred workers, resulting from deficient diets, with diets sufficient in calories, vitamins, and minerals produced full rehabilitation, even for heavy industrial work (171). Exaggerated fatigability may also be due to hyperinsulinism. Atropine prevents the drop of blood sugar and abolishes excessive fatigue in these patients (172). Workers with gastritis, anemia, or nervous disorders are considered as poor risks (4).

Physiological aspects of industrial accidents.—There are two main aspects of the problem of industrial accidents: (a) the special hazard of industrial occupations (type and conditions of work), and (b) individual proneness to accidents. The number of disabling work injuries during 1941 increased by 46 per cent over 1940, compared to an employment increase of 21 per cent and an increase of employee working hours of 28 per cent, so that frequency rate (average number of injuries per million hours worked) increased by 14 per cent (173). The total time lost is estimated to be equivalent to full time employment for a year for 800,000 workers. The increase in the frequency rate is attributable to the influx of large numbers of inexperienced workers, crowding of workers, failure of safety activities to keep fully abreast of the war program, more complicated war work, introduction of new processes and substances, less maintenance time for machines running for twenty-four hours, etc. During the preceding years, 1934 of 1939, the frequency rate of accidents showed a continuous decline due to safety activities (173). The fall of the fatality rate of coal and metal mining has dropped by about 40 per cent during the period from 1911 to 1935 (174). In a number of metal industries introduction of the safety program reduced the accident rate by 46.6 per cent (175). The increase of the accident rate from 1939 to 1941, however, did not nullify the success of the preceding years of safety work, the rate being still below the level of 1933 and 1934. The increase in 1941 was most pronounced in metal working machinery, electrical equipment, rubber tires, and the shipbuilding industry. However, in aircraft, petroleum, and explosive industry the trend was reversed (173). This shows that general war conditions need not increase the accident rate. It is interesting that in

January to February 1943 among seven industry groups within the lowest range of frequency rate (of less than ten) there were three composed of plants directly engaged in producing ordnance material (176). This shows that safety can be practiced under extreme pressure for production. Increase of production may be accompanied with reduction of the accident rate as shown in a study in fourteen thousand plants (177). The positive correlation between production rate and accident rate, as found during the last war, is no inherent characteristic and unchangeable feature. In England the influence of the war effort on the accident rate was not particularly noticeable (178). In this country the reports for the first six months of 1942 (179) show, for the first time since the beginning of the defense program in 1940, a significant reduction of the number of accidents per one million hours worked; in nineteen states the average increase of employment was 25 per cent, that of accidents only 17 per cent over the first six months of 1941. There were wide variations in different states, probably to a large extent due to expansion of different types of industries. The frequency rate varies between different occupations, the extremes being the telephone workers (2.4) and logging (96.3). Even in the same industry there are wide variations characterizing the risk in different jobs (173). In eleven different departments of a steel mill for the year 1940 the frequency rate (per million working hours) varies between 0.50 and 5.91 (21). There was no correlation between serious accidents involving lost time and minor accidents treated by first aid, so that probably different factors are responsible for either type. The frequency rate in manual workers exceeds that of nonmanual workers by three times. While in the manufacture of lumber products, small shops had a lower frequency rate than larger plants (180), the reversed relationship was observed for shipyards (181). Injuries occurred less frequently in summer than in the other seasons. In regular day shift workers the peak of injuries occurred on Mondays and in the third working hour, with a second and smaller peak during the eighth hour. The evening and night shifts had their greatest volume in the first working hour. If fatigue be a major factor in the accidents of shipyard workers, another distribution should be expected. Although it is accepted that the accident frequency rate increases with increase of the number of working hours, especially when the number of working hours is excessive (182, 183), this relationship is not always as clear. Tiffin (21) holds that it may be due to psychologi-

cal factors rather than to fatigue. Toro (184), using the Donaggio reaction as fatigue test (see page 546,) found 14 per cent of men who had accidents were fatigued. The higher rate of positive Donaggio reaction after the accident might also be due to other factors than fatigue. Introduction of safeguard mechanisms have reduced but not eliminated accidents in punch presses. Some of these mechanisms failed to consider important features of muscular coordination, as shown by Mogilanskaya (185) in a classical study using Bernstein's kymocyclographic method. From several variables (speed, duration, and spatial relationships of the movements of hands, feet, and the press) the accident risk was calculated as a coefficient, values under 1.0 expressing definite accident risk. Considered also was the maximum speed of hand movements, with which the worker could expose himself to injury at any phase of the work, in spite of existing safety devices. By means of this method different types of presses and protection mechanisms were analyzed. The traumatic phase of a friction press with a rate of sixty-six beats per minute exceeds that of an excenter press with a rate of 166 beats per minute by three to five times. The accident rate of punchers using a hand lever was 13 per cent, those operating a pedal was 31 per cent and with automatic machines 35 per cent (186).

One of the most fundamental discoveries of the recent twenty years is individual accident proneness. As little as 10 per cent of a group of workers may be responsible for as much as 75 per cent of the total number of accidents (187). Accident proneness is a relatively stable quality obeying fairly definite laws. Those who sustain an undue number of one kind of accident also sustain an undue number of other kinds. In nine thousand sheet and tin mill workers individual accident proneness was responsible for about 60 per cent of all accidents among the most accident-prone group (21). Tiffin holds that in plants with high special accident risks the personal factor is less important than in plants where the working conditions are not hazardous. This assumption would lead to the paradoxical conclusion that elimination of accident-prone workers is more important for nonhazardous occupations than it is for hazardous jobs.

Individual accident proneness might be due to quite different factors, for instance, to psychological factors (21, 188). Also age and sex have influence on the individual accident proneness. The frequency rate of accidents declines with age or years of service

(2, 56, 189), so that the influence of age may reflect training and experience. The accident rate is high in very young workers engaged in wood industry (190). However, in some plants an increase of the frequency rate of accidents with age has been found (21). The duration of disability and the rate of permanent orthopedic impairment increases with age (191).

The industrial accident frequency rate of women is lower than that of men, while the rate of nonindustrial injuries is somewhat higher (189, 191, 192, 193). With the increasing employment of women their accident rate increases, but is still significantly lower than that of men (193, 194). England has had the same experience (195). An important specific cause of individual accident proneness is faulty vision. If out of 13,000 workers of a steel mill those who failed in four vision tests had been eliminated, the lost time accident rate would have been reduced at least 25 per cent (21). Another important cause of accident proneness is a dissociation between the speed of visual perception and the speed of muscular coordination. Individuals whose level of muscular action is above their level of perception are more prone to accidents than those persons who can perceive quicker than they can react (196). Alcohol in small dosage by decreasing visual perception and increasing speed of movements might increase accident proneness (197). Accident proneness may also be due to vasomotor instability, as shown by Lahy (198) in investigations on accident-free and accident-prone bus conductors, using Gomez's piezographic method.

The tests for screening accident-prone workers are still in the experimental stage. Even so, a fairly good percentage of accident-prone workers can be recognized by a battery of tests involving rapid and accurate coordination of hand and eye, mechanical aptitude, etc. Their validity is much greater among skilled than among unskilled workers (188). Using such tests for elimination of accident-prone workers, the percentage of men dismissed for bad accident records has been reduced from 14 per cent to less than 1 per cent in the Milwaukee Railway and Light Company (199).

Absenteeism.—The absence incidence due to sickness exceeds the accident incidence by fifteen to twenty times, while the lost time due to sickness exceeds the lost time due to industrial accidents by seven times (200) and equals about ten billion man hours loss per year in this country. Absenteeism is not necessarily due to sickness; this is especially true for short time absenteeism; ab-

senteeism "from personal reasons" is estimated as high as 50 per cent of the total absenteeism (189). Absenteeism exceeding seven days represents more accurately sickness absenteeism, but consideration only of absences of more than seven days would eliminate about 80 per cent of the total absenteeism. Disabilities of short duration are more likely to respond to efforts of prevention or control (189). Sickness absenteeism depends on a multitude of socioeconomic and psychological factors, benefit compensation systems, medical care, epidemics, etc. (201). Within the scope of this review only those factors can be considered which involve some physiological aspects (type of work, fatigue, age, sex, working conditions, etc.). The frequency rate (average annual number of absences per one thousand workers) has to be discriminated from the severity rate (average number of days lost per absence). There is some evidence that they depend on different factors, for instance, age increases the severity rate more than the frequency rate (189). The order of nine companies, arranged according to increasing frequency rate, was not the same when similarly arranged according to severity (201). During a five year period the frequency rate of absences of seven days or more among 30,000 male industrial workers showed a downward trend, the severity rate an upward trend (202).

The trend of sickness absenteeism (over seven days) of 250,000 male members of industrial sick benefit associations increased from 1939 to 1942 (189, 203). The first quarter of 1943 shows a substantial increase of sickness absenteeism, compared with the first quarter of 1941 or 1942 (204). In England the increase was still more pronounced, but it was somewhat lower in 1941 than in 1940 (205). In General Motors the increase of absenteeism from September 1941 to October 1942 was due only to absences of less than a week (167). In a public utility plant (206) the absenteeism from 1938 to 1941 was highest in 1939 (including absences of one day or longer). This shows that increase of absenteeism is not necessarily correlated to emergency conditions. The increase of absenteeism during the war might be due to a multitude of factors; in general, the absenteeism during a period of expansion exceeds the rate during stagnation (207) or depression (208); it does not necessarily indicate deterioration of health, but might be regarded as a natural corollary of any improvement in the standard of living. Of course, there are limits; for instance, the sickness rate of persons on relief exceeds that of the working population to such a

degree that workers, previously on relief, show a higher rate for some time even after employment (167).

Is the increase of absenteeism possibly due to increased fatigue from excessive working hours or from the speed-up of production? There is evidence that any disease increases fatigability, because the same compensation mechanisms are used in disease and muscular exercise (157). However, there is no direct evidence yet available that fatigue decreases the resistance power against disease, although it may seem logical to assume a mutual relationship. Reduction of excessive working hours (seventy a week) to an average of fifty-five a week reduced absenteeism during the First World War in England (24, 25). After the fall of France, prolongation of the working day and abolition of holidays increased absenteeism in England to such extent, that Sunday was reintroduced as a legal holiday and the working day shortened, although not to the prewar level (24). Increase of daily working hours from nine to twelve hours increased absenteeism in an American Munition Plant 9.3 per cent in the first and 12.2 per cent in the second year after introduction (209). There is complete agreement that excessive working hours (limits sixty weekly hours for men, fifty-five for women) increase absenteeism (210, 211). There are no sufficient data regarding optimum working hours of less than fifty-five per week (207). Gosden (212) found in eight hundred workers in England an increase of absenteeism from 3.2 per cent to 6.2 per cent from 1939 to 1941, parallel to an increase of weekly working hours from 49.5 to 52.7, although the type of work did not change. It is questionable whether the slight increase of three hours a week is responsible for an increase of absenteeism of almost 100 per cent. In the graphs presented by Court (207) there is no consistent relationship between weekly hours and absenteeism within the range from forty to fifty-five hours. Perhaps, the heaviness of work has influence on this relationship (213). In England only 30 per cent of men and 10 per cent of women are working longer than ten hours a day, and in this country the percentage is probably still lower. It is not probable therefore, that the increase of absenteeism is due to excessive working hours. There is evidence that six working days a week is the optimum and that abolition of the Sunday as a holiday increases absenteeism (24, 207). Split shift workers have unusually good attendance records (167). The absenteeism increases with age, especially in regard to the severity rate (189, 207, 214), so that the total rate is about twice as high in the age group

of fifty to fifty-nine compared with the age group of twenty to forty. The increase of absenteeism with age is more pronounced with men than with women (215), so that the discrepancy between men and women is greatest in the younger age groups. The rate of absenteeism of female workers exceeds that of male workers by 50 to 300 per cent, especially due to the prevalence of short time (one to three days) absences; the excess can be explained only partially by dysmenorrhea (189, 192, 203, 207, 216, 217, 218). Married women are reported to have a higher absenteeism rate than single women (207), but this has not been confirmed (192). For the question whether the higher absenteeism rate of women is an inherent characteristic, it is pertinent to compare the rate of employed women and men with that of unemployed men and women. Recently a large group (665,060 white males and 239,107 white females), canvassed in eighty-three cities relative to absences of seven days or longer, has been made available (219). The difference of the sickness rate between unemployed men and women (nonrelief, work relief, direct relief) was even higher than was the difference between employed male and female workers. It seems, therefore, that the greater rate of absenteeism among women is an inherent characteristic and that accumulated fatigue from a greater amount of extra work is a secondary factor.

The published material on sickness absenteeism of colored workers is scarce. Former reports showed a higher rate for negroes, but as the occupations and socioeconomic status of negro and white males became more nearly alike, the excess of the frequency rate of disabilities among negroes tends to decrease, if not to disappear entirely (189).

Several studies concern the influence of occupations on the rate of absenteeism. The absenteeism was higher at fixed pace conveyor belt work than among other types of work in three Canadian plants (220). The age standardized frequency rate as well as the annual number of days lost was highest in laborers and lowest in office workers among male employees of the soap industry, the ratio being 4.3:1 (217). Female packing machine operators had a higher rate than female office workers, the ratio being 2.24:1, compared to a ratio of male packing machine operators to male office workers of 3.3:1. Male office workers had the lowest rate also among employees of mail order stores, although the difference to other jobs was much less; but female office workers had a rate slightly higher

than other female employees (218). In the meat packing industry male and female office workers had the lowest absenteeism rate (221), but show a higher increase of absenteeism with age than the average. The total disability rate for white employees was highest under conditions of humid heat, second highest for extreme dry heat, and lowest for usual environmental conditions while that of negro workers is not higher under conditions of humid heat. Although the total rate of absenteeism is higher in negroes, it is much lower in high humidity than that of white workers (221). It appears that negroes can stand humid heat better. This would agree with physiological findings (97). The increase of absenteeism with age is most pronounced in high humidity. It appears that an age over thirty-five is a handicap for high humidity (221). Workers of the iron and steel industry showed a lower sickness rate than the average of all industries during the period from 1921 to 1938, although the pneumonia rate and that of rheumatic diseases was higher (216). The notable excess of pneumonia in 1941 and 1942 in iron and steel workers might be partially attributed to the extraordinary increase in the number of such workers (222, 223).

Due to restricted space the distribution of sickness absenteeism among various disease groups can not be discussed in detail. Occupational diseases play a minor role. The greatest part is due to respiratory diseases, including the common cold, the percentage distribution being influenced by age and sex (189). Respiratory diseases are especially responsible for short absences of a few days. It is estimated that a loss of 45,000,000 days of work per year in this country is due to common cold representing a wage loss of \$400,000,000, \$250,000,000 for medical care, and \$400,000,000 for disarrangement of work routine (224). In England about 1,000,000 workers lose one day per year owing to common cold (226). Even a slight common cold without increase of body temperature may interfere with production by increasing fatigability, as shown by the depression of the fusion frequency of flicker (225). Vaccine treatment decreased the severity rate, but not the frequency rate of absences due to common cold (227). However, there is no effective prevention against acute respiratory disease (228). Keefer holds that as a whole cold vaccines or vitamins failed to reduce absenteeism due to common colds; however, ultraviolet irradiation of the air or propylene glycol vapor give more encouraging results (229). The influence of physical fitness and exercise on the suscepti-

bility to colds has been recently reviewed (230). One of the most interesting recent discoveries is the individual sickness proneness. Of a group observed during 1935 to 1940 10 per cent of the workers accounted for 50 per cent of all absences (189). Increasing age tends to reduce the number of sickness attacks per year, but to increase the average length of each disability. In eight Wisconsin plants (193) 9 per cent of all male employees were responsible for 47 per cent of all absences, 33.7 per cent were responsible for all absences. Similar findings were obtained for female workers. To recognize the factors responsible for proneness to sickness absenteeism is one of the most important future problems of industrial medicine. Proneness to accident and proneness to illness do not seem to be related; women have a higher absenteeism rate and lower industrial accident rate than males. Dunbar's findings point in the same direction; out of 1,500 hospital patients, the group of coronary and angina patients had a previous illness history (excluding accidents) about five times as great as that for fracture patients (corrected for age distribution), and only 6 per cent had previous accidents. In contrast 72 per cent of the fracture patients had had one or more previous accidents (231).

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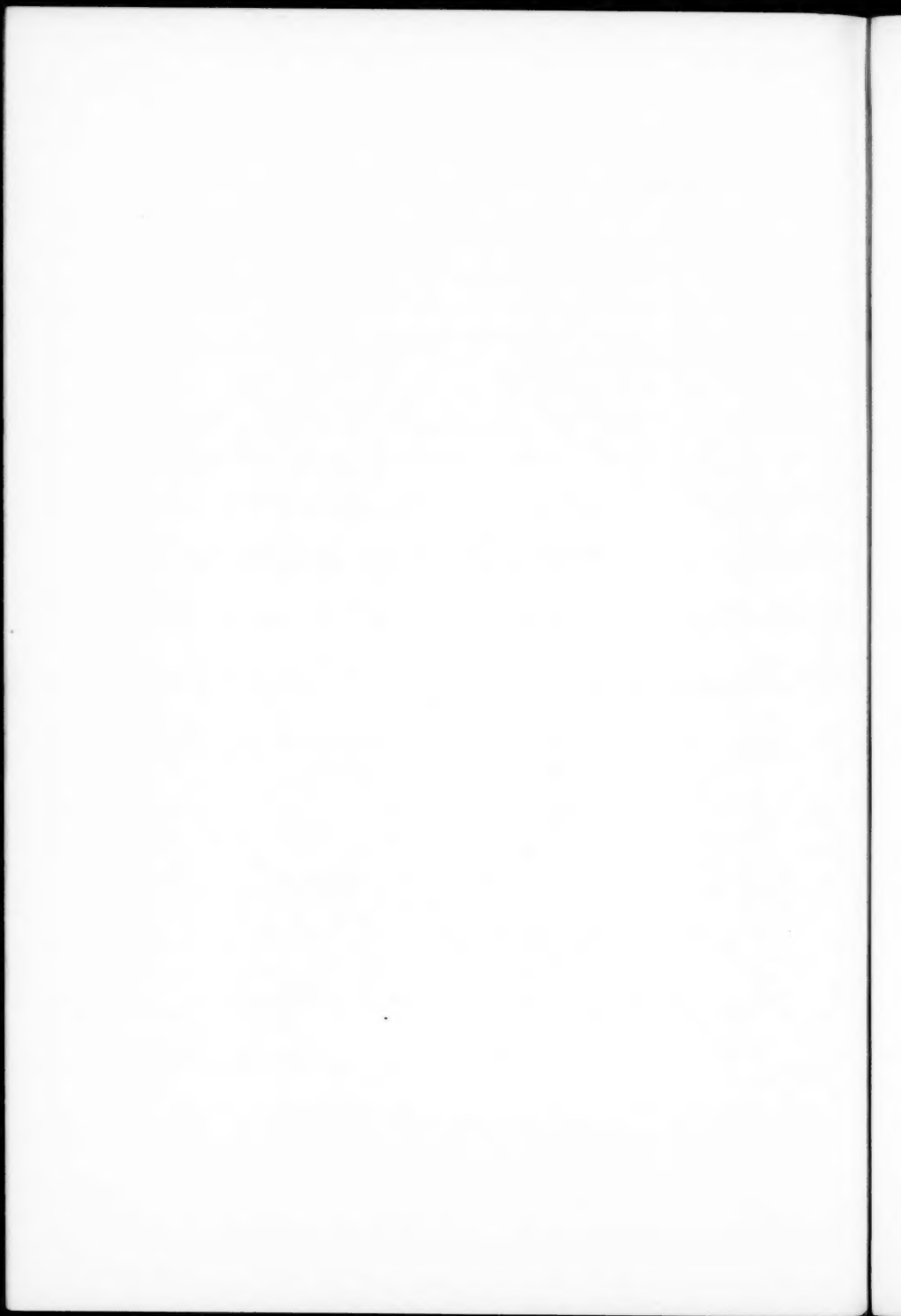
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ADDENDUM

Due to the fact that the author's corrected galley proof arrived from England after page proof had been returned to press, we find it necessary to add here the following footnote which ordinarily would have appeared at the bottom of page 430:

More recently E. B. Astwood (*J. Am. Med. Assoc.*, **122**, 78-81, 1943) and R. H. Williams & G. W. Bissell (*Science*, **98**, 156-58, 1943) have successfully treated human thyrotoxicosis by the daily administration of thiourea or 2-thiouracil. Williams & Bissell found that thiouracil treatment does not prevent the increase in basal metabolic rate which normally follows administration of desiccated thyroid. This finding supports Astwood's suggestion that this type of goitrogenic agent interferes with the process of synthesis of thyroid hormone.



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